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American Journal of Diseases of Children

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OBSERVATIONS ON THE HEALTH AND GROWTH OF CHILDREN IN AN INSTITUTION *

L. EMMETT HOLT, M.D., AND HELEN L. FALES

NEW YORK

Through the courtesy of the trustees of a semicharitable institution for children of both sexes, we have had the opportunity to make observations for thirty-one months on the growth and nutrition of the children who were inmates. The data obtained have furnished some very interesting statistics on the growth and general condition of children living under institutional conditions.

THE INSTITUTION

The institution was a Roman Catholic home and school for poor children, conducted by Sisters of a French order. During the first twenty months of our study, it was housed in an old-fashioned building occupying a plot about 100 feet square in the heart of the uptown business section of New York, which had been its home for over fifty years. This building was surrounded by tall office buildings, which cut off from it much light and fresh air. It was, therefore, dark and rather gloomy, though scrupulously clean. The refectories and kitchen were in the basement, requiring artificial light. The schoolrooms and dormitories were on the upper floors and had light on at least one side. The children were divided according to age into three groups for each sex. They slept in dormitories accommodating from twenty to thirty children each. Each child had a separate cot. The bathing facilities consisted of shower baths and wash bowls. The playgrounds, one for the boys and one for the girls, consisted of two small yards in the rear of the building, enclosed by high brick walls, the size of each being about 30 by 40 feet.

A summer home in the country was maintained where each child spent one month, some of the children going in July and the rest in August. A few who were in special need of the vacation were allowed to remain through the two months.

In January, 1922, the institution was moved to a country estate about 30 miles from New York. The new home consists of several buildings

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* Received for publication, April 19, 1923.

* From the laboratories of the Rockefeller Institute for Medical Research and the Babies' Hospital.

providing ample space and plenty of light and air. There are playrooms in the dormitory building and in the schoolhouse. There are two large outdoor playgrounds, one for each sex, equipped with swings, slides, etc.

INMATES

Most of the children of this institution are not of the poorest classes, since as a rule a moderate fee is charged for their care. A few of the children were orphans; many were half-orphans, and some had both parents. The nationalities were chiefly French, Spanish, Italian and Irish. On the first examination and at subsequent observations, the children were with but few exceptions in excellent physical condition. They were happy and gay, not suffering in the least from institutional repression, although they were living under strict regulations. The schoolwork is the same as that of the public school. No systematic physical education is given, although the girls and small boys have lessons in folk dancing and dramatics.

The ages of the boys ranged from 4 to 14, the girls from 4 to 16. Many of the children remain in the institution for the entire period covered by the age limit. Some remain only a few months. There was, consequently, considerable change, from time to time, in the material on which our study was based.

GENERAL HEALTH

The general health of the children is supervised by a visiting physician. He gives each applicant for admission a complete examination, and excludes defective children and those acutely ill or suffering from contagious diseases. Malnutrition is not a cause for exclusion, but is rather made a reason for admission. The rule of the institution is to quarantine for at least two weeks each child admitted. Minor ailments are treated by one of the sisters, who acts as nurse and administers cathartics when necessary. About once in two weeks each child in the institution is given a dose of cascara sagrada as a precautionary measure. In the spring all children receive a tonic for a few weeks. Common colds are dealt with promptly by administration of a hot drink and an active cathartic.

The effectiveness of the general routine which is followed in the institution is manifest in the always excellent physical condition and the good digestion of the children. As an example, the cleanness of the tongues of the children was especially noteworthy. On one examination day special observations were made of the condition of the mouths. Of 144 children, only twenty showed even the slightest coating of the tongue, and only five showed marked coating, these being mostly older girls who were working in the kitchen.

During our study there was surprisingly little illness of any kind in the institution; no epidemics of any sort occurred, and almost no cases of serious illness. There were no deaths in the institution during the period of observation. One child was removed to a hospital suffering from appendicitis, from which he died. The infrequency of any important illness is further shown by the fact that in all the twenty-two weighing days, on each of which an average of 135 children were examined, there were only seventeen absences on account of illness.

When the institution was in New York many of the children had decayed teeth, fully 30 per cent. showing this condition at first examination. Since the removal to the country, much of this has been corrected. Adenoids and hypertrophied tonsils were found in about the usual frequency—nearly 30 per cent. of the children. During our period of study forty of the children had tonsillectomies. The children as a rule had excellent color, especially after removal to the country.

In general, it may be said that the surprisingly good physical condition of these children reflects great credit on the management of the institution. The impression is prevalent that children living in institutions decline in general health and vitality, and that their growth and physical development are inhibited. Our observations of these children show that this is not a necessary result, and that the contrary may be true. The carefully controlled life in a properly managed institution, the regular hours, the good food and the lessened chances of infection, because the children do not come in contact with other children as do those who attend public school, make it possible to keep these children in excellent health, in fact, in much better condition than children in most private homes.

ROUTINE

The children rise at 6 a. m., and wash and dress in silence. At 7 they have breakfast, which, like all meals is taken without talking. This practice has been followed because it was found that the children ate better than when talk and play were permitted. Like most children, they eat rapidly, seldom taking over twenty minutes for a meal, even a dinner of three courses. From 9 a. m. until 12 m., they are in school. At 12 m., dinner is served, and school follows from 1 to 3 p. m. From then until supper is play time. The older girls spend a portion of this time in sewing. The younger children have supper at 5 p. m. and go to bed at 6. The older children have supper at 7 p. m. and go to bed at 8. The older girls help in the general housework, and in the country the older boys assist about the grounds.

While in the city, the only outdoor exercise, except the time spent in the playyards, was a trip to Central Park on Sunday morning. The children walked to and from the park—about 1 mile—and played there for about one hour. In the country the children do considerable walking about the grounds, since the school is some distance from the other buildings. They play out doors each afternoon, the weather permitting.

From a hygienic point of view the conditions in the country are a great improvement over those in New York, but, as will be shown later, this change in environment apparently has had little effect either on health, weight gain, or general appearance of the children, possibly because the physical condition was so good while they were living in the city.

DIET

Until about one month before our observations were begun the regular diet included little milk, although in other respects it was excellent. Tea and cocoa containing a very little milk had been given. Some additional milk had been used in the preparation of other food. A large amount of meat had been provided, it being served once and sometimes twice a day, and meat soup was served twice a day. A month before our observations were begun the addition to the diet of a pint of milk daily for each child had been made. The amount of meat served was somewhat reduced and no meat or meat soup was served at supper.

Table 1.—*Menu for a Week*

	Breakfast	Dinner	Supper
MONDAY	Bread and butter Cocoa	Meat soup Mutton stew Bread and cake	Milk soup Bread and jelly Fruit
TUESDAY	Oatmeal Bread and jelly Cocoa	Meat soup Roast beef, cabbage Bread, bananas	Baked beans Bread and butter Milk
WEDNESDAY	Cornflakes Milk and bread	Soup with carrots, onion Veal, tomato stew Bread and cake	Rice pudding Bread and jelly Milk
THURSDAY	Hominy Milk Bread and jelly	Meat soup Boiled beef Potatoes Bread and apples	Tapioca pudding Bread and butter Cocoa
FRIDAY	Oatmeal Bread Cocoa	Julienne soup Fish or egg Bread and bananas	Milk soup Baked beans Bread and jelly
SATURDAY	Bread and butter Cocoa	Meat soup Mutton Lettuce Bread and prunes	Bread pudding Apple sauce Bread and milk

Table 1 gives a typical weekly diet after these changes had been made. This dietary, with only minor variations, has been used throughout the period of our study.

The cocoa served at breakfast was made with milk without adding water. At supper the children either drank milk plain or took it in the form of milk soup, that is, hot milk with some seasoning and with bread added. Little butter was used. Soups were made from meat stock with the addition of vegetables, and were served with large pieces of stale bread added. The dessert was usually fresh fruit or small sweetened rolls or cakes, which were often donated by hotels or restaurants. The children have always received throughout the year a fair amount of green vegetables; since the removal to the country, this has been somewhat increased. All the children received the same food, the quantity only being varied according to the age. Bread was allowed *ad libitum,* and the amounts consumed were astonishing. Each child usually ate at least two large pieces at each meal and many, especially the larger boys, took four or five slices. In addition to the amount taken at meals, a large piece was usually served to each child in the afternoon.

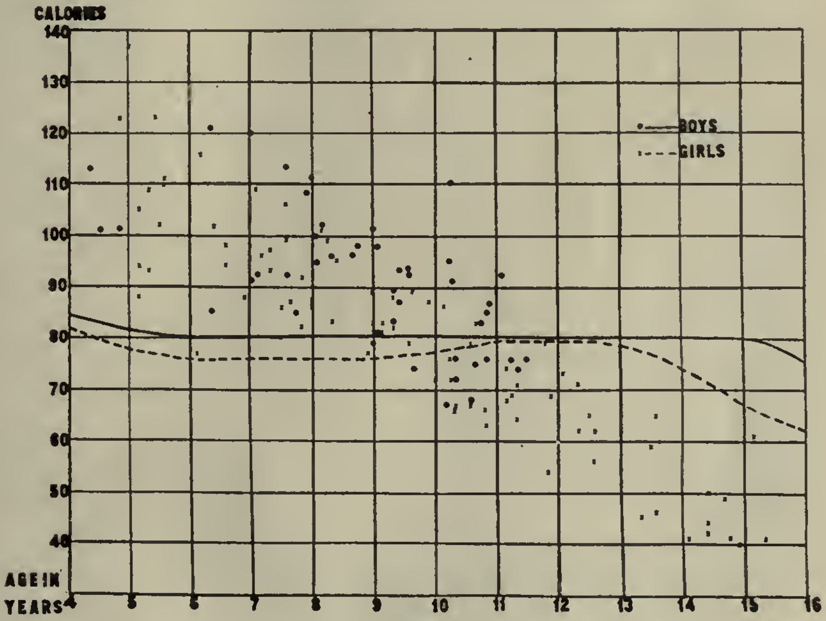

Chart 1.—Calories per kilogram taken by 129 children.

In October, 1920, the approximate amount of food taken for two consecutive days by each child then in the institution was ascertained. From the data obtained the caloric intake of each child, the percentage of distribution of the calories and the amount of fat, protein and carbohydrate were calculated. As a whole, the total caloric intake was high, except in the case of some of the older girls. It is suspected, however, that the amounts recorded for this group did not represent their total food intake, since they were working in the kitchen and refectories and had ample opportunity to obtain additional food.

The average distribution of the calories taken was: fat, 22 per cent.; carbohydrate, 61 per cent., and protein, 17 per cent. This distribution is somewhat different from what we have considered ideal: viz., fat, 35 per cent.; carbohydrates, 50 per cent., and protein, 15 per cent. The fat furnished too low a proportion of the total calories, and the carbohydrate too high a proportion. The supply of vitamin A was therefore probably not up to the average. The carbohydrate intake was very high. This was mainly due to the large amounts of bread consumed. The protein intake was higher than the average. The protein intake per kilogram was liberal. About 56 per cent. was animal protein and 44 per cent. vegetable protein, a somewhat lower proportion of animal protein than the optimum. However, the generous total protein intake undoubtedly compensated for this. The supply of mineral salts, especially calcium, was possibly low, since only 1 pint of milk was given.

Table 2.—*Typical Diet Sheet of a Medium Sized Boy* (Average Amount of Food Taken for Two Days)*

		Calories			
Article of Food	Amount	Fat	Carbohydrate	Protein†	Total
Milk	16 oz.	149	94	69	312
Butter	1½ tsp.	56	0	0	56
Cocoa	1 tsp.	7	4	2	13
Cake	0.5 piece	15	54	8	77
Gravy	2 oz.	11	3	2	16
Jelly	¼ oz.	0	25	0	25
Sugar	2 tsp.	0	49	0	49
Apple	50 gm.	2	22	1	25
Vegetables, mixed	1 tbsp.	1	5	1	7
Cabbage	4 oz.	1	2	4	7
Tomato	3 oz.	2	18	4	24
Meat	3 oz.	99	0	90	189
Soup	10 oz.	11	14	54	79
Rice pudding	4 oz.	62	141	35	238
Tapioca pudding	4 oz.	76	121	31	228
Bread‡	12 pieces	43	783	135	961
Total food		535	1,335	436	2,306
Calories per kilogram		23	57	18	98
Calories per pound		10	28	9	44
Distribution of calories		23	58	19	
Grams daily		58	326	106	
Grams per kilogram		2.4	13.8	4.5	
Grams per pound		1.1	6.3	2.0	

* W. A., aged 8 years and 9 months, weight, 52 pounds (23.6 kg.), height, 47 inches (117.5 cm.); average weight for height; undersize for age.

† Proportion of animal protein, 56 per cent.; of vegetable protein, 44 per cent.

‡ Amount includes that added to soup, tomato, etc.

Chart 1 shows the calories per kilogram taken by forty-six boys and eighty-three girls. The line shown on the chart is that previously estimated by us as a desirable average.[1]

It will be seen that the children up to the age of 10 years took considerably more than the theoretical requirement, while those over 10 often received less. This was largely due to the manner of serving the meals to the children. The food for the entire dining room was brought to the table in large containers, and a sister served it to the children, making some variation in amount according to the size of the child. By this practice, however, the smaller children received *proportionally* more than the larger ones. For example, a girl weighing 40 pounds (18 kg.) would receive at least half as much food as a girl weighing over 100 pounds (45.4 kg.). Of such items as fruit, cakes, etc., as well as milk, practically the same quantity was given to all the children, regardless of size. Therefore, since the amount of food taken was governed not by the desires of the children but by the judgment of the sister who served, the values are not to be taken as a guide for the *normal* caloric requirement. It is interesting, however, to note that the young children took eagerly so much food, and with apparently no ill effects.

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[1] Holt, L. E., and Fales, H. L.: Food Requirements of Children; Total Caloric Requirements, Am. J. Dis. Child. **21**:1 (Jan.) 1921.

Table 2 gives the form in which the diet of each individual was studied.

TABLE 3.—*Number of Observations*

Number of Observations	Boys	Girls	Total
18 – 22	21	41	62
12 – 17	18	18	36
7 – 11	37	54	91
4 – 6	17	18	35
1 – 3	58	64	122
Total	151	195	346

TABLE 4.—*Duration of Observation*

Duration	Boys	Girls	Total
2 yrs. – 2 yrs. 7 mos.	21	48	59
1½ – 2 yrs.	14	7	21
1 yr. – 1½ yrs.	23	41	64
6 mos. – 1 yr.	29	30	59
3 – 5 mos.	12	15	27
Under 3 mos.	30	43	73

OBSERVATIONS ON GROWTH

During the thirty-one months of our study, the children were weighed at frequent intervals, usually once a month, and the height was measured about once in three months. In all, 2,995 observations on weight were made on 346 children, 151 boys and 195 girls. The number of observations of each child varied according to the length of stay in the institution. Table 3 gives an idea of the number of observations for each child, and Table 4 the approximate duration of the period of observation of each child.

The height was measured without shoes. The weights were taken without shoes, and in the usual indoor clothing. Heavy jackets or sweaters were removed. The children did not wear an institutional uniform, but there was much more uniformity in clothing than would be found in a public school group. The clothing was simple, not excessive in weight, and varied very little for children of the same age and size.

Various weighings were made of the average clothing worn in the winter and summer, not including shoes, coats and sweaters. This weight of the clothing was practically the same for boys and girls. It was found that for the large children, that is, those over 60 pounds (27.2 kg.) in weight and over 50 inches (125 cm.) in height, the average weight of winter clothing was 2 pounds; that of the summer clothing, 1.5 pounds. For the smaller children, weighing from 40 to 60 pounds (18 to 27.2 kg.) and ranging from 35 to 50 inches (88 to 125 cm.) in height, the average was 1.5 pounds for winter clothing and 1 pound for summer clothing. The weights taken have all been reduced to net weight by making the deduction for clothing just mentioned. The purpose of this was to secure a more accurate comparison of the weights taken at different seasons. This correction for clothing is, of course, not absolutely accurate for children of all ages. However, since the same reduction to net weight was made in the successive weighings of each child, the gain or loss in weight is exact.

TABLE 5.—*Distribution of Children According to Nationality*

Nationality	Number of Boys	Number of Girls	Total
American	9	14	23
French	27	30	57
Italian	37	47	84
Spanish	30	32	62
Irish	23	39	62
Balkan	6	10	16
Central European	19	23	42
Total	151	195	346

The data obtained at the initial examination of each child have been analyzed to determine the relation of the weight to height, weight to age and height to age, and the variation of each of these relations according to nationality.

The racial distribution is shown in Table 5. The Central European group includes mostly Germans, a few Russians, Austrians, Scandinavians, Bohemians, one Hungarian and one Pole. The American group includes children born in this country and whose parents were also born here, but whose parentage was so mixed as to eliminate racial differences. Many of the children classed in the national groups were born in this country, but the parents were not; or the racial influence was so obvious that the classification was evident.

Relation of Weight to Height.—This relation on the first examination is shown in Charts 2 and 3. The solid line shows the standard weight for height and is based on the values given by Holt and Howland.[2] These values are derived from the figures obtained by ten dif-

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[2] Holt, L. E. and Howland, J.: Diseases of Infancy and Childhood, Ed. 8, New York, D. Appleton & Co., p. 23.

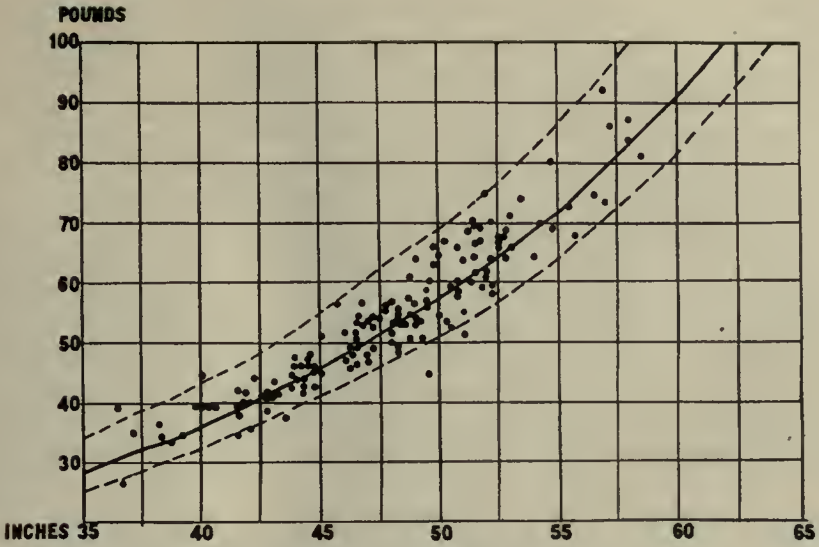

Chart 2.—Relation of weight and height (151 boys).

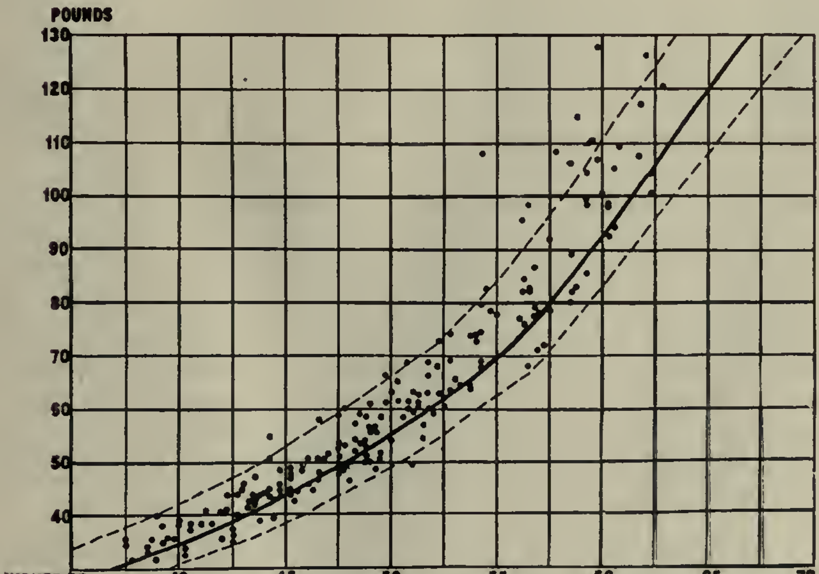

Chart 3.—Relation of weight and height (195 girls).

ferent authors and are based on more than 100,000 observations. The dotted lines in each chart mark the zone including the weights of boys and girls, respectively, 10 per cent. below and 20 per cent. above the standard weight for height. The charts show that the children of the institution were with very few exceptions near average weight for height, the tendency being slightly above the average.

A doubt has been expressed by some writers as to the propriety of using a single weight-for-height standard for different races. It was found that nationality had no apparent effect on the weight-height ratio of the children studied in the institution. Table 6 shows the exact relation of the height to weight and the influence of nationality on that ratio.

The adoption of a definite limit for the percentage below average weight as an evidence of malnutrition has frequently been questioned. It has been argued that, if this is done, some perfectly healthy children might be classed with those clearly not normal, especially if any definite variation according to race does exist. The most commonly accepted limits used in classifying children as normal in weight for height are from 10 per cent. below the average to 20 per cent. above. It is interesting to apply this standard to the group of children studied by us. There were only six boys and one girl who were more than 10 per cent. below average weight for height. Since there were so few underweight children, the details regarding them may be of interest. It will be noted that only one of these children had been in the institution more than one month when examined.

Table 6.—*Relotion of Weight to Height in Different Nationalities*

	Normal Weight for Height (10% Below to 20% Above Average)		Under Weight for Height (More than 10% Below Average)		Overweight for Height (More than 20% Above Average)		
Nationality	Number	Percentage of Total	Number	Percentage of Total	Number	Percentage of Total	Total Number of Children
American	23	100	0	0	0	0	23
French	50	88	3	5	4	7	57
Italian	82	98	0	0	2	2	84
Spanish	56	90	2	4	4	6	62
Irish	58	94	0	0	4	6	62
Balkan	15	94	0	0	1	6	16
Central European	39	93	2	5	1	2	42
Total	323	93	7	2	16	5	346

Case 1.—Boy, French, aged 7 years and 4 months, examined six days after admission, and nutrition graded as II, had no physical defects. He remained in the institution only twelve days.

Case 2.—Boy, French, aged 7 years and 4 months, examined fourteen days after admission, and nutrition graded III, suffered from rachitis of long standing, enlarged glands, bad teeth and scaly skin. Only one observation was made.

Case 3.—Boy, Spanish, aged 4 years and 9 months, examined two weeks after admission, was mentally defective. He gained 3 pounds in the twelve months following the first examination.

Case 4.—Boy, Spanish, aged 7 years and 7 months, examined one month after admission, and nutrition graded II, was highly nervous, with enlarged adenoids and tonsils (no operation was performed). He gained 5½ pounds in the next six months.

Case 5.—Boy, German, aged 5 years and 3 months, examined two weeks after admission, and nutrition graded II, was one of twins (see Case 6). He had rickets of long standing, bad teeth and frequent minor illnesses. Inheritance was bad. He gained 5 pounds in weight and three-fourth inch in height in fourteen months.

Case 6.—Boy, German, aged 5 years and 3 months, one of twins (Case 5), presented the same clinical picture as did his brother. He weighed a little more than the brother on admission, but made less progress. He gained 2 pounds in weight and 1.75 inches in height in fourteen months.

Case 7.—Girl, French, aged 8 years and 6 months, examined two months after admission, and nutrition graded II, had bad teeth. She gained 1 pound in three months.

This proportion of underweight children is much smaller than that reported in most groups of schoolchildren. Whether the ample food and the excellent hygiene of the institution account for this is an interesting question. All but seventy-two of the children when first examined had been resident for at least one month and all but four for at least two weeks. It is probable that any previously existing underweight may have been corrected by the excellent food and hygiene even in as short a time as one month. It is the usual experience that children who are much below weight make a rapid initial improvement when they are given a proper diet and are placed in better environment. In selecting children for admission, preference was given by the admitting physician to those obviously in need of improved living conditions. In consequence, it is fair to assume that there had been some improvement in weight during the first few weeks of residence.

Sixteen children were considerably overweight; that is, they were more than 20 per cent. above the average weight for their height at first examination. Nine of these sixteen overweight children were girls between 11 and 15 years of age, years in which a marked degree of plumpness is frequent. Of the sixteen children, four gained more than the average in the succeeding months; five gained at the average rate; two gained less than average, and one lost weight. Four did not remain in the institution long enough for subsequent observation. It is evident, however, that the condition of overweight had no definite relation to their further progress in growth.

Relation of Height to Age.—Wide variation of height in relation to age is seen in healthy children of all races. While the relation of height to exact age has little significance in individuals, it is interesting when groups are considered. Charts 4 and 5 show the relation of height to age. The children as a group, especially the girls, were short, as compared to the averages established from statistics obtained by the examination of mixed groups of American schoolchildren. Of 149 boys, sixty-four (43 per cent.) were about average height for age, or more than average height, and eighty-five (57 per cent.) were not up to the average height for age. Of 195 girls, sixty-five (33 per cent.) were about average height for age, while 130 (67 per cent.) were under average height for age.

Table 7 gives the distribution of these values according to nationality. The Spanish children were the nearest to the average in height-age relation. The Italian children were shortest. The Irish as a group were also short. It was of interest in studying the height to consider separately the children who had been resident in the institution for a long period before our observations were begun, since the diet previously had been notably deficient in calcium because of the small amount of milk given. Since the calcium supply is of undoubted importance in growth in height, it is not surprising that these children were short. Of eighty-nine children who had been resident in the institution for more than one year previous to our investigation, only eighteen (20 per cent.) were of average height for age, while seventy-one (80 per cent.) were under average height. Of these children, twenty-eight were as much as 4 inches (10 cm.) (almost two years' growth) under the average height for age, while ten were over 6 inches (15 cm.) under average height.

TABLE 7.—*Relation of Height to Age in Different Nationalities*

	Above or About Average Height for Age		Under Average Height for Age		
Nationality	Number	Percentage of Total	Number	Percentage of Total	Total Number of Children
American	11	48	12	52	23
French	23	40	34	60	57
Italian	22	26	62	74	84
Spanish	33	53	29	47	62
Irish	20	33	41	67	61
Balkan	3	19	13	81	16
Central European	17	41	24	59	41
Total	129	37	215	63	344

Relation of Weight to Age.—The relation of weight to age showed, as would be expected, very wide variation, but on the average the children were near the usual weight for age. This was due to the fact that, although short, most of these children were of more than average weight for height.

Progress.—Most of the children who were under observation for a long enough period to allow any conclusions in regard to their progress

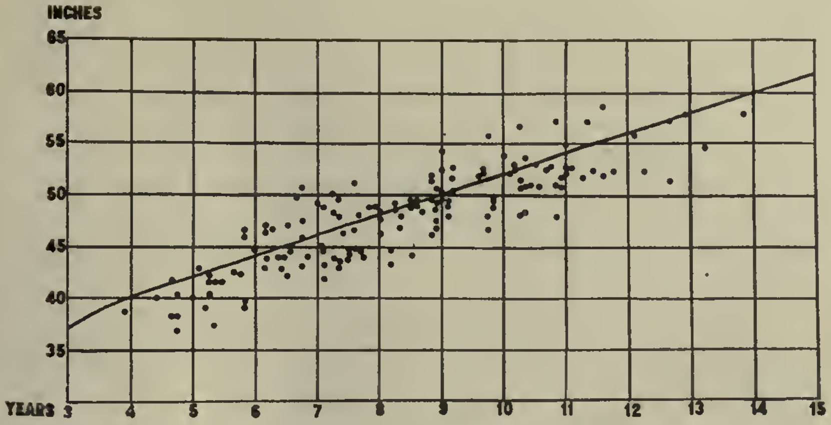

Chart 4.—Relation of height and age (149 boys).

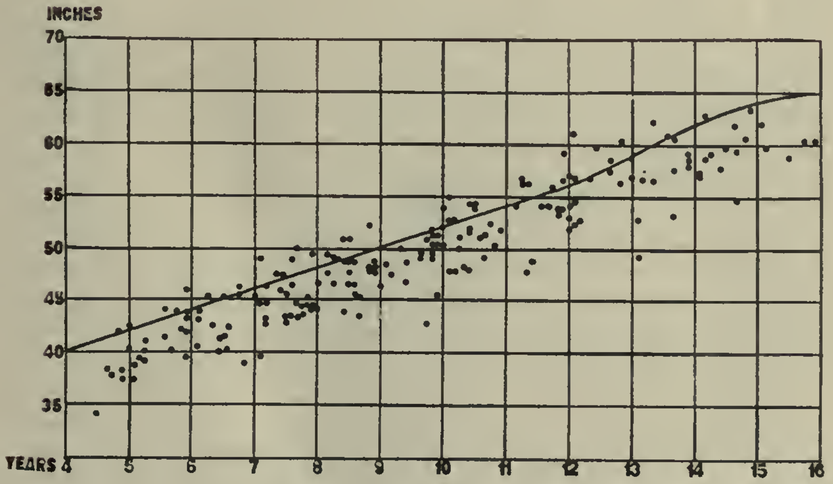

Chart 5.—Relation of height and age (195 girls).

in growth gained well and steadily in both weight and height. A critical survey of the rate of growth, however, showed that many of these children failed to make normal progress.

Table 8 shows the rate of growth of 148 children who were under observation for one year or more. The greater number of the boys gained weight normally. Two thirds of them made also a normal gain in height. A little more than half the girls gained weight normally, and only one half made an average gain in height. When it is recalled that many of the children, especially the girls, were overweight or of average weight for age, these figures for rate of gain in weight are what might have been expected.

The progress in height is, however, a different matter. Most of these children were under average height for age, and it might have been expected, therefore, that in their good environment and with their liberal food allowance the height gain would proceed at more than average rate. There may be several reasons why this did not occur.

TABLE 8.—*Progress in Weight and Height*

		Weight				Height			
		Progress Normal or Better than Normal		Progress Less than Normal		Progress Normal or Better than Normal		Progress Less than Normal	
	Total Number	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
Boys.........	55	44	80	11	20	36	65	19	35
Girls.........	93	54	58	39	42	48	51	45	49
All.........	148	98	66	50	34	84	57	64	43

It is possible that the diet, which included only 1 pint of milk daily, was not adequate in mineral salts, especially in calcium. The observations of some recent writers, notably Sherman,[3] indicate that since the other articles of food contain but little calcium, 1 quart of milk daily is needed by the growing child to supply a sufficient amount. Again, it is one of the observed facts in regard to growth that short children grow more slowly and tall children more rapidly than the average; so that, as a rule, short children become short adults, and tall children, tall adults. Many of these children belonged to short races, the Italian and French; but the short stature and slow growth were found in the case of the Irish, who are not racially short. Whether it is possible to stimulate an established slow rate of growth by special diet is an interesting question. It has been proved possible within certain limits to do this with animals whose growth has been retarded by insufficient mineral salts, provided the retardation has not persisted too long.

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[3] Sherman, H. C., and Howley, E.: J. Biol. Chem. **53**:375 (Aug.) 1922; J. Home Econ. **14**:413 (Sept.) 1922.

Table 9 shows the average six months' increment in weight and height, according to age, of the children studied. For comparison, there is given the average six months' increment (Holt and Howland, p. 22), which has been derived from large numbers of observations. The standard values for six months are not absolutely exact, since they have been obtained by dividing the usual yearly increment by 2, to obtain a value for a six months' period. The difference is unimportant. It is evident that the six months' growth of these children was, on the average, very near the normal. The fact that the average height gain was so near the normal is especially interesting in view of the observation previously made that many of the children gained in height at less than the average rate. It is evident that the others gained at enough more than the usual rate to compensate for those whose gain was less, thereby making the average very close to the values usually found.

TABLE 9.—*Average Yearly Increment in Weight and Height*

	Boys					Girls				
		Weight Gain (Pounds)		Height Gain (Inches)			Weight Gain (Pounds)		Height Gain (Inches)	
Year of Age	Number of Cases	Average	Normal*	Average	Normal*	Number of Cases	Average	Normal*	Average	Normal*
4 – 4.5	1	1.0	2.0	1.25	1.25	0	...	2.0	....	1.25
4.5 – 5	1	3.0	2.0	1.25	1.25	1	3.0	2.0	0	1.25
5 – 5.5	3	1.5	2.0	1.25	1.00	6	1.3	2.0	1.0	1.00
5.5 – 6	6	2.1	2.0	1.00	1.00	9	1.9	2.0	1.1	1.00
6 – 6.5	4	3.1	2.0	1.10	1.00	11	1.9	2.0	1.0	1.00
6.5 – 7	7	2.9	2.0	1.10	1.00	15	1.9	2.0	0.75	1.00
7 – 7.5	8	2.0	2.4	1.00	1.00	14	2.6	2.25	1.00	1.00
7.5 – 8	11	3.0	2.4	1.00	1.00	18	2.1	2.25	0.95	1.00
8 – 8.5	11	2.8	2.6	0.75	1.00	21	2.0	2.5	0.90	0.80
8.5 – 9	13	2.9	2.6	1.00	1.00	20	2.9	2.5	1.0	0.90
9 – 9.5	20	2.2	3.0	1.00	1.00	21	1.6	2.6	0.95	1.10
9.5 – 10	14	2.9	3.0	1.00	1.00	13	2.8	2.6	1.1	1.10
10 – 10.5	13	2.4	2.5	0.90	0.8	19	3.4	3.2	1.0	1.00
10.5 – 11	16	3.4	2.5	1.00	0.9	18	2.2	3.3	1.0	1.00
11 – 11.5	11	3.8	3.2	1.10	0.9	12	4.8	4.7	1.2	1.25
11.5 – 12	6	3.9	3.3	1.00	0.9	9	2.3	4.8	1.15	1.25
12 – 12.5	4	6.0	4.0	1.35	1.0	8	5.4	5.25	1.15	1.00
12.5 – 13	..	...	...	....	....	9	6.5	5.25	0.90	1.00
13 – 13.5	..	...	...	....	....	8	2.5	4.8	0.95	1.00
13.5 – 14	..	...	...	....	....	6	7.1	4.7	1.0	1.00
14 – 14.5	..	...	...	....	....	7	3.0	3.8	0.95	0.60
14.5 – 15	..	...	...	....	....	9	5.3	3.7	0.63	0.60
15 – 15.5	..	...	...	....	....	5	3.3	3.0	0.45	0.40
15.5 – 16	..	...	...	....	....	1	2.5	3.0	0.50	0.30

* Holt and Howland: Diseases of Infancy and Childhood, p. 22.

Seasonal Growth.—A good deal of interest has been shown recently with regard to the variation in growth in different seasons of the year. The figures published by Porter [4] indicate that there are such variations, and that these are quite regular; viz., that the increase in weight during the six months from June to December far exceeds that in the six months from December to June. Gebhart[5] has recently published figures showing exactly what percentage of the annual gain in weight may be allocated to each of the calendar months. In his theoretical schedule, 60 per cent. of the gain for the entire year is made in the four months August to November, inclusive. The observations analyzed by him were quite numerous, but since his conclusions were based, partly upon the growth of one group of children who were followed for only four consecutive months and partly upon the growth of other groups who were followed but eight months, they seem hardly warranted by his facts.

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[4] Porter, W. T.: Am. J. Physiol. **52**:121 (May) 1920.

Seasonal variations in growth have been ascribed to changes in environment, in activity and in diet, and to minor illnesses. It was thought that observations on the children studied by us might furnish some interesting data on this point, because their life was so nearly the same for the entire year. Their diet was known both qualitatively and quantitatively, and seasonal changes in diet were slight. Except for a single month in summer, their activity varied but little during the different periods of the year. Their environment remained the same. Besides, as a group they were remarkably free from serious or even minor illnesses.

We have analyzed the weight records with reference to the following points: (1) a comparison of the winter and spring period (December to June) with the summer and autumn period (June to December); (2) the average gains made in each calendar month by boys and girls, and (3) the average gains for each successive month of the children who were followed for long periods. The average gain of the girls in 187 summer periods was 3.26 pounds; and in 144 winter periods, 3.34 pounds. The average gain of the boys in 113 summer periods was 3.50 pounds, and in eighty-five winter periods, 2.44 pounds. In the girls, there was therefore little difference between the summer and winter periods, the winter period showing, however, a slight increase. In the boys, the average summer gain was greater by one pound.

In graphic Chart 6 are shown the average gains by calendar months for boys and girls. Not all of the children were observed throughout the entire period, some being studied for two and a half years, some for only one year and some for only a few months. There were not less than forty-three and not more than fifty-five boys weighed each time, and not less than sixty-eight and not more than ninety girls. In 1920, there was a period of four months, June to September; in 1921, one of three months, July to September, and in 1922, one of two months, August and September, in which monthly weighing could

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5. Gebhart: Height and Weight as an Index of Nutrition, Bull. New York Ass'n for Improving Condition of the Poor, 1922.

not be made. The total weight gain for these periods has, therefore, been divided equally into monthly increments. Accordingly, the values for these months, as shown on the charts, are somewhat arbitrary.

There was much less variation shown in the gains of the girls than in those of the boys. The loss in weight in May and June, 1922, for the boys, and in June and July of the same year for the girls may be, in part, explained by more than usual activity, since this was their first warm season in the country, removal from the city having occurred in the previous January. This explanation is not entirely satisfactory, as the girls made good gains in May, the month in which the greatest loss for the boys is recorded.

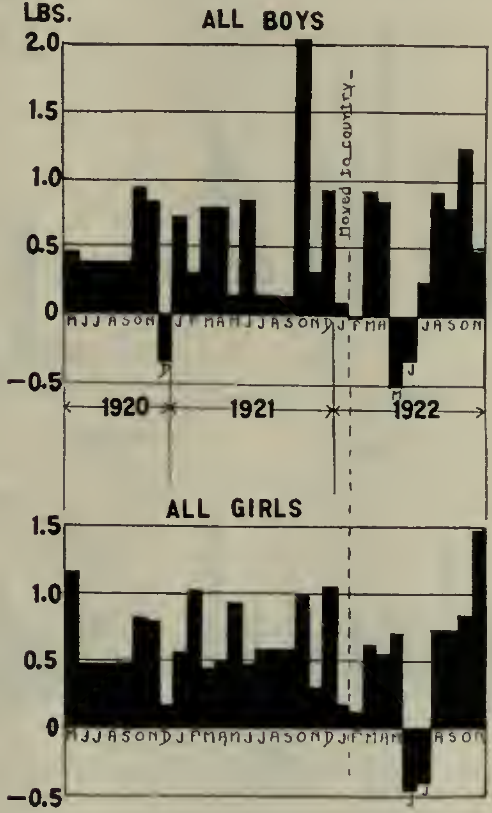

Chart 6.—Average gain in weight by months.

About the only conclusion that can be drawn from these charts is that monthly gains are not at all regular even in healthy children with the same food, the same habits, and the same environment, and that periods of two or three months of little gain are likely to be followed by a period of great gain, as is strikingly shown by the boys in 1921.

The difference in gain during the same calendar months of successive years is also striking. June, November and December, especially, show wide variations in different years for both sexes.

The great variation in monthly gains is even better brought out in Chart 7, where are shown the average gains for the children who were observed continuously during practically the entire period of our study. Although this is not a large group, the results are very striking. In considering these observations, the fact that we have grouped together children of different ages does not vitiate any conclusions, since the same children were observed throughout the entire period.

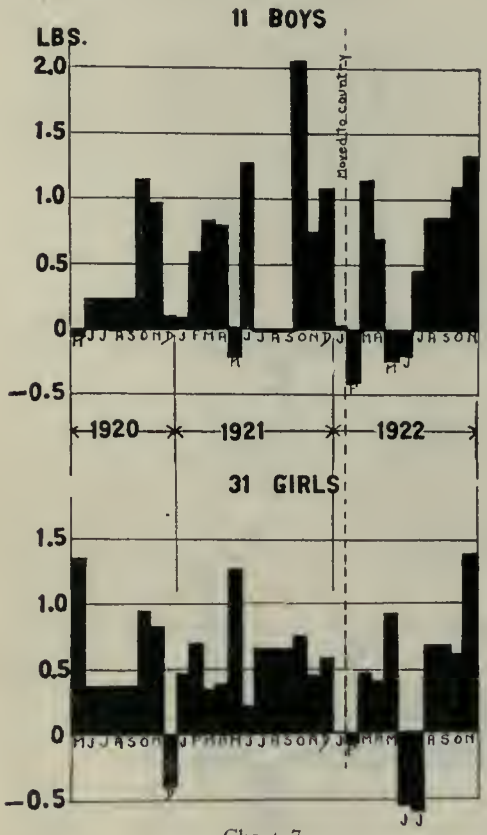

Chart 7

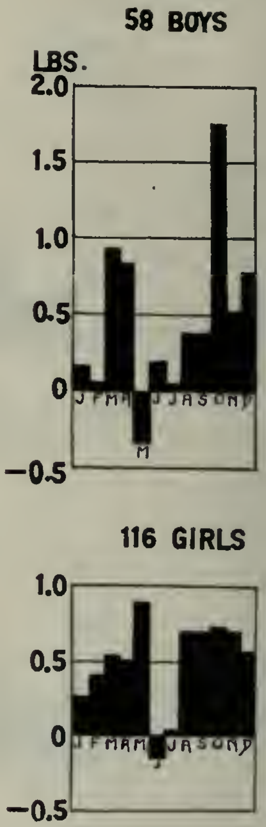

Chart 8

Chart 7.—Average monthly weight gain in children observed for thirty-one months.

Chart 8.—Average monthly weight gain in children observed for one year.

Chart 8 gives the average increment in weight for each calendar month for fifty-eight boys and for 116 girls who were under observation continuously for one year.

It seems quite clear that it cannot be laid down as a rule that a healthy child gains a certain amount each month, nor that at any particular month or period the increase in weight is regularly more rapid, and at another period regularly slower, than the average rate for the year. The tendency, however, is certainly toward a more rapid gain in the autumn months. The fact that the children studied by us, in regard to whom seasonal differences in diet and environment were insignificant, showed a marked, but irregular variation in monthly gain, would seem to indicate that the seasonal variation found by others is not due chiefly to the factors mentioned. It seems probable that a difference in activity may account for some of the difference between the summer and autumn gains, since the marked activity of the vacation months is usually reduced when the children spend four or five hours a day in school.

The one thing which was found to be fairly regular in these children was the annual increment. This was quite uniform. In this respect, our observations are in close accord with those of others. The regularity of the annual increment is of great significance in establishing a standard for healthy growth.

It seems of interest to append a few individual growth charts which are typical of certain groups of the children studied.

Chart 9 shows the growth curves for two years of a girl, 10 years old at the beginning of observation, who was of average weight for height and average size for age. The net progress in both weight and height in the two years proceeded at the normal rate, although there were marked fluctuations in weight, there being several periods of four or five months in which no net gain occurred. It will be noted that these periods of slow gain had no regular relation to season.

Chart 10 shows the growth curves for two and a half years of a girl, 8 years and 6 months old at the beginning of observation, who was at that time of average weight for height and average size for age, but who grew at better than the average rate. The fluctuations in the weight gain are especially marked. There are two periods in which there was continuous weight loss for about five months, followed, however, by a rapid gain in weight. This case illustrates especially the possible fallacy in judging the condition of the child and the progress in nutrition by following the weight for a short time.

Chart 11 shows the growth of a boy, 9 years and 6 months old at the beginning of observation, followed for two years, who was of average weight for height and a little more than average size for age, and whose growth proceeded at about the usual rate. Especially noteworthy is the marked drop in weight without evident cause in June and July of the second year, followed by a rapid increase which more than compensated for the decline.

Chart 12 shows the growth of a boy, 11 years old at beginning of observation, followed for over two years. He was undersize for his age at the beginning of observation, and grew at considerably more than the average rate. The progress in this case was regular. This case, like the others presented, illustrates especially the fact that gains in weight and height usually proceed together.

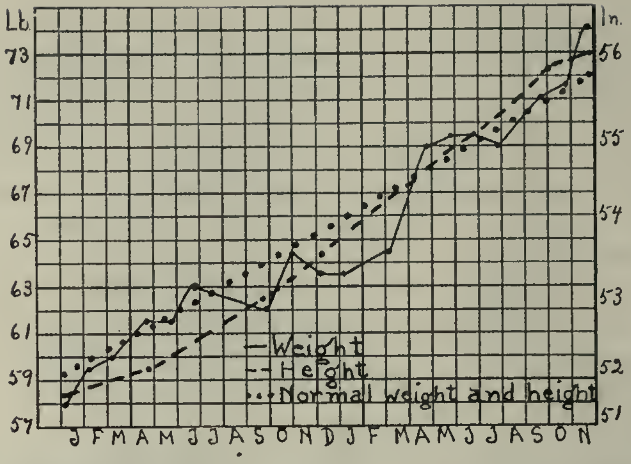

Chart 9.—Gain in weight and height of A. P., girl, French (initial age, 9 years and 11 months).

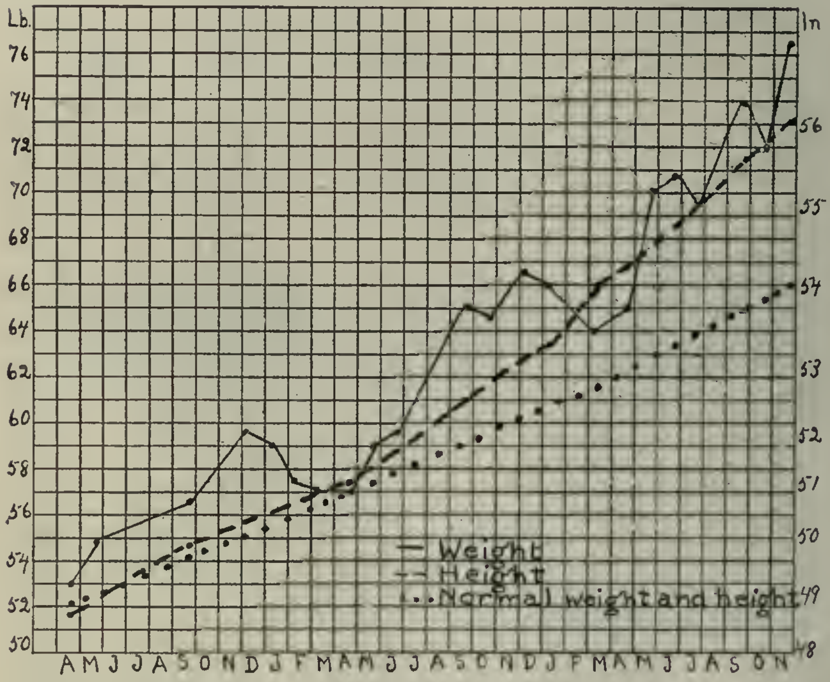

Chart 10.—Gain in weight and height of E. M., girl, Austrian (initial age, 8 years and 5 months).

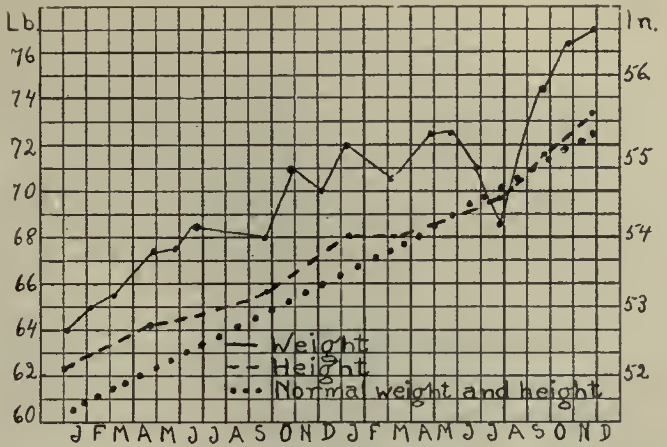

Chart 11.—Gain in weight and height of M. C., boy, French (initial age, 9 years and 8 months).

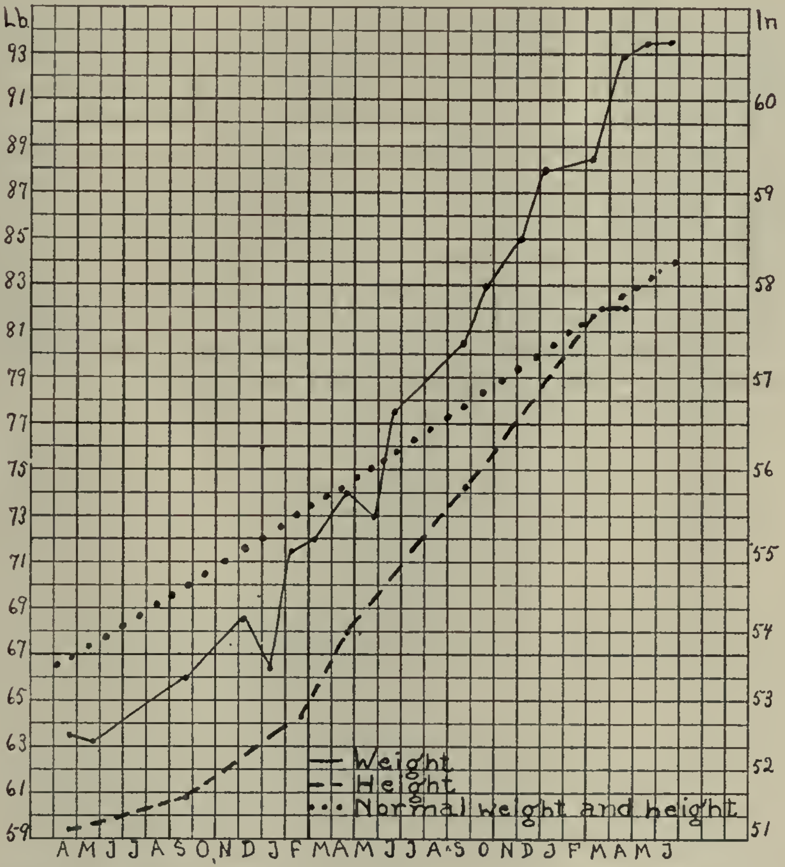

Chart 12.—Gain in weight and height of D. C., boy, Italian (initial age, 10 years and 10 months).

SUMMARY

1. The observations show that strikingly good health and excellent nutrition can be maintained in an institution. The factors which contributed to this result were: (1) regularity in habits of eating and in sleep, rest and exercise; (2) a liberal but simple diet, and (3) freedom from contact infections. This shows what might be the case in private families provided the same rules of simple and regular living were observed.

2. In the distribution of fat, protein and carbohydrate in the diet, there existed a considerable deviation from what is considered optimum. In spite of this, health and digestion remained excellent, and the gains in weight were satisfactory. This shows how wide a deviation is consistent with health, provided certain essentials in the diet are furnished, and that regularity in habits is maintained.

3. Growth possibly would have been better if more milk had been allowed, furnishing more fat, more vitamin A and more calcium.

4. The usually accepted standard for normal nutrition, that is, inclusion in this group of those who were not more than 10 per cent. below the average weight for height, was found to hold good when applied to these children in spite of the differences of nationality.

5. While these observations are not numerous, they were continued long enough to show very clearly that in this group there were no regular seasonal variations. This is especially significant since the living conditions were so nearly uniform throughout the year.

6. The annual rate of gain was remarkably regular, though the monthly gains showed wide fluctuations, with no regularity whatever. This emphasizes the necessity of prolonged observations before a stationary weight can be considered significant.

THE LEUKOCYTE COUNT IN THE NEW-BORN WITH DEHYDRATION FEVER *

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The purpose of these observations was to determine whether or not an increase in the leukocyte count accompanies the transient fever which frequently occurs in the new-born during the first week of life. It has long been thought that this fever may be due to dehydration. Holt,[1] in 1895, pointed out that it occurred in infants who had lost a great deal of weight (a part of which, presumably, is due to water loss), and that it could be cured by the administration of fluids. In a recent paper,[2] it was shown that the transient fever of the new-born is associated with a decrease in the plasma water, as indicated by an increase in the protein concentration of serum, determined refractometrically. The oral administration of warm water results in a drop in the temperature to normal within from thirty to ninety minutes. This is accompanied by an increase in the water content of the blood, as shown by a fall in the serum protein concentration and the red cell count.[3] In infants with fever due to infections, the serum proteins are not increased, and no significant fall in temperature follows water gavage despite the fact that this procedure is followed by an increase in the blood water.

Bacon, Novy, and Eppler [4] in a study of the leukocyte count in dehydration fever in animals, induced fever by rapidly injecting hypertonic salt solutions into the femoral vein of dogs after the manner described by Balcar, Sansum and Woodyatt.[5] At the end of the first hour, they found a slight leukopenia with a relative increase of the small lymphocytes. Following this there was a steady rise in the leukocyte count to levels far above normal. The increase was almost wholly confined to the polymorphonuclear leukocytes.

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* Received for publication, May 5, 1923.

* From the Pediatric Division of the New York Nursery and Child's Hospital, and the Department of Pediatrics, Cornell University Medical College.

1. Holt, L. E.: Inanition Fever in the Newly Born, Arch. Pediat. **12**:560, 1895.

2. Bakwin, Harry: Dehydration Fever in the New-Born, Am. J. Dis. Child. **24**:508 (Dec.) 1922.

3. Bakwin, Harry; Morris, R. M., and Southworth, J. D.: To be published.

4. Bacon, D. K.; Novy, F. O., and Eppler, H. H.: Factors in Leukocytosis, Arch. Int. Med. **30**:229 (Aug.) 1922.

5. Balcar, J. O.; Sansum, W. D., and Woodyatt, R. T.: Fever and Water Reserve of the Body, Arch. Int. Med. **24**:116 (July) 1919.

Bacon and his co-workers point out the similarity in the leukocytic reaction in experimentally produced dehydration fever and in the fever following the injection of a foreign protein. They believe that the mechanism by which fever and leukocytosis are produced is identical in both conditions. According to them, the acute water shortage in dehydration fever results in an accelerated protein metabolism with the greater productions of its by-products, such as urea and creatinin. As evidence for this hypothesis, they point to the rise in the nonprotein

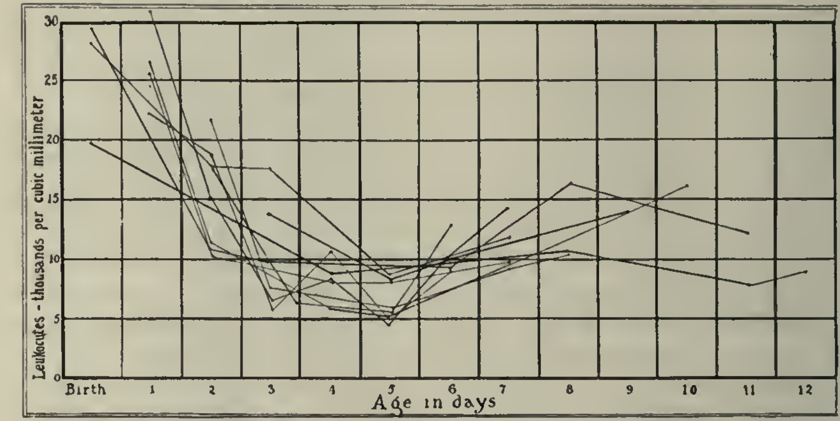

Chart 1.—Variations in the leukocyte count of afebrile new-born infants during the first few days of life.

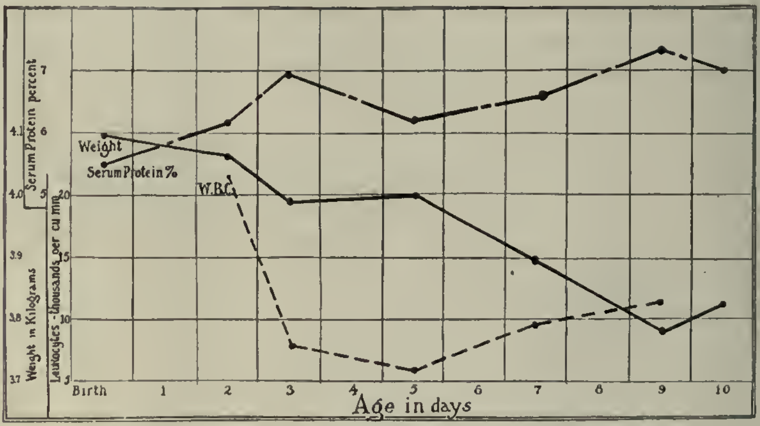

Chart 2.—The lack of relationship between variations in blood concentration and the leukocyte count is shown. As the weight falls, the percentage of serum protein rises, indicating a diminution in the plasma water. The increase in weight is accompanied by a return of the serum proteins to normal. The physiologic drop in number of the leukocytes occurs during the first five days, despite the increase in blood concentration.

nitrogenous constituents of the blood that occurred regularly in their dogs with dehydration fever.

Rietschel[6] has recently called attention to a nonbacterial form of fever which he calls "dynamisches Eiweissfieber." He produced it in infants by feeding concentrated diets of high protein content, and he ascribes it to the increased metabolism resulting from the high specific dynamic action of protein. Because of the low fluid content of the diet, sufficient water is not available for the elimination of the

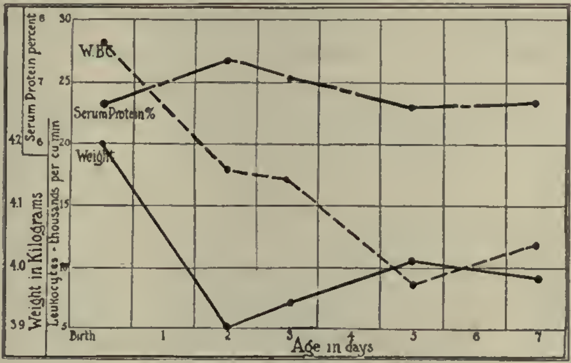

Chart 3.—The lack of relationship between variations in blood concentration and the leukocyte count is shown. The fall in leukocytes during the first week and the slight rise during the second week are entirely independant of the blood concentration, as measured by variations in the percentage of serum protein.

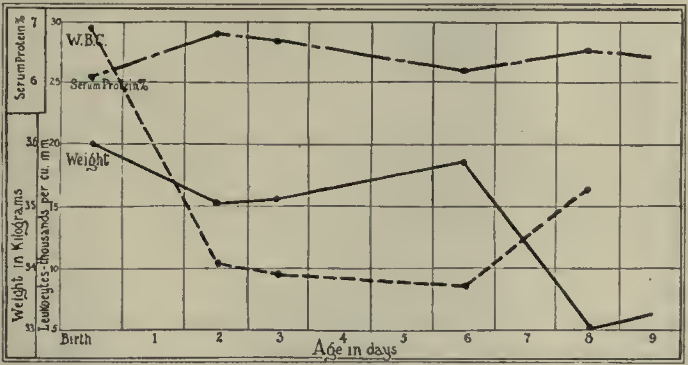

Chart 4.—The lack of relationship between variations in blood concentration and the leukocyte count is shown. The fall in the number of leukocytes during the first week and the slight rise during the second week are entirely independent of the blood concentration, as measured by changes in the percentage of serum protein.

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6. Rietschel: Dynamisches Eiweissfieber, Klin. Wchnschr. **2**:9 (Jan. 1) 1923.

increased amount of heat from the body surface by evaporation. (Somewhat similar examples of fever of nonbacterial origin in infants have been described by Finkelstein,[7] Holt and Levene[8] and Benjamin.[9])

No figures are available concerning the leukocyte count in new-born infants with dehydration fever. Repeated determinations were made on a large series of infants during the first ten days of life. Blood was obtained from the toe from three to four hours after a feeding, and counts were made in the usual manner. Blood for serum protein concentration was collected at the same time. The technic employed was similar to that described in previous papers.[10] The temperature was taken at the time of puncture.

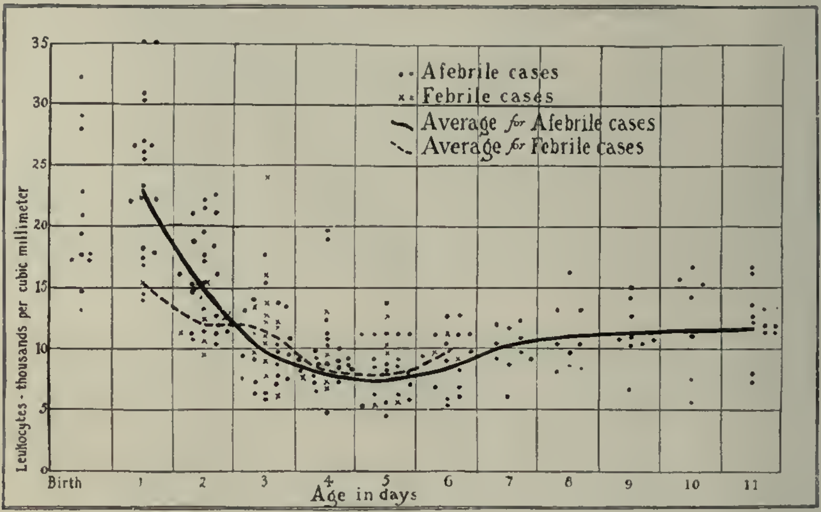

Chart 5.—The leukocyte count in afebrile and febrile new-born infants. The average curves are almost identical.

Because of the wide variations in the number of leukocytes during the first weeks of life, a group of afebrile babies was studied. Our results correspond fairly closely to those of previous observers.[11] On the first day (Table 1 and Chart 1), the white cells are markedly increased in number, usually ranging between 20,000 and 25,000 per cubic millimeter. They fall rapidly and reach the adult level on the fifth to the seventh day. A rise to 10,000 or 12,000 follows, during the second week.

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[7] Finkelstein, H.: Ueber alimentärisches Fieber, Deutsch. med. Wchnschr. **35**:190, 1909.

[8] Holt, L. E., and Levene, P. A.: The Influence of High Protein Feeding on the General Metabolism, on the Intestinal Flora, and on the Body Temperature of Infants, Am. J. Dis. Child. **4**:265 (Nov.) 1912.

[9] Benjamin: Weitere Untersuchungen zum Eiweissnährschäden des Säuglings, Jahrb. f. Kinderh. **80**:545, 1914.

[10] Bakwin, Harry: Dehydration in the New-Born, Am. J. Dis. Child. **24**:497 (Dec.) 1922.

[11] Von Reuss, A. R.: Diseases of the New-Born, London, 1921, p. 42.

It has been suggested that the leukocytosis in the new-born is due to an increase in the blood concentration. Repeated simultaneous observations on the white cell count and the serum protein concentration show that the variations in the leukocytes are entirely independant of changes in the blood concentration determined refractometrically (Charts 2, 3 and 4).

Table 1.—*Daily Variations in the Leukocyte Counts in Afebrile and Febrile New-Born Infants*

	Afebrile				Febrile			
	Number of Cases	Leukocytes per C.Mm.			Number of Cases	Leukocytes per C.Mm.		
Age, Days		Maximum	Minimum	Average		Maximum	Minimum	Average
Birth	12	32,400	17,200	20,300	0	......	......	......
1	19	35,400	16,800	22,500	1	15,400	15,400	15,400
2	21	22,000	10,400	15,600	7	14,300	9,500	12,100
3	21	17,700	5,700	10,000	15	24,000	6,000	12 500
4	23	19,000	4,800	9,300	5	13,000	6,600	8,700
5	20	13,600	4,500	7,800	5	12.900	5,500	8,700
6	15	12,900	5,200	9,200	3	11,200	9,500	10,100
7	10	12,100	6,000	10,200				
8	9	16.300	8.000	10,600				
9	9	15,000	6,600	10,800				
10	7	16,200	5,700	12,100				
11	12	16,500	7,300	12,300				
12	4	19,900	9,100	12,500				

Table 2.—*Temperature and the Leukocyte Count in New-Born Infants*

Temperature		Number of Cases	Leukocytes per C.Mm.		
Centigrade	Fahrenheit		Maximum	Minimum	Average
36.1	97	34	30,800	4,800	10,800
36.6	98	139	35,400	5,400	11,800
37.2	99	35	22,400	7,200	13,200
37.8	100	15	24,000	5,500	11,000
38.4	101	8	15,400	9,500	11,900
38.9	102	10	15,900	6,000	11,300
39.5	103	5	16,100	7,600	12,100

The daily leukocyte counts in new-born infants with and without fever are presented in Table 1. It will be seen that the daily variations in the white cell counts of babies with fever correspond closely to the variations of those without fever. This is graphically represented in Chart 5.

In Table 2, the leukocyte counts are arranged according to the temperature. No relationship was found between the degree of fever and the leukocyte count.

SUMMARY AND CONCLUSIONS

1. At birth, the leukocytes are increased, the counts usually ranging between 20,000 and 25,000 per cubic millimeter.

2. There is a rapid fall to normal during the first week, followed by a rise, usually starting on the fifth day, to from 10,000 to 12,000.

3. The variations in the leukocyte count are not due to changes in the blood concentration.

4. There is no change in the leukocyte count in new-born infants with dehydration fever, the daily average in those with fever corresponding closely to that in babies without fever.

THE BASAL METABOLISM OF PREMATURITY

III. METABOLISM FINDINGS IN TWENTY-ONE PREMATURE INFANTS *

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The object of the present study, commenced two years ago, was to gain further knowledge of the premature infant, and, if possible, to establish the physiologic basis for the nutritional requirements of these infants.

A review of the literature showed that few studies had been made on the metabolism of premature infants. Some of these studies cannot be accurately interpreted because of differences in technical methods. This is particularly true of Rubner and Langstein's [1] and Weiss' cases.[2] The investigations of Hasselbalch,[3] although carried out with a slightly different technic, are comparable, because they were obtained under basal conditions. The cases reported by Fleming, Murlin and Marsh [4] and Benedict and Talbot [5] are strictly comparable. So far as we know, there have been no comprehensive studies of the basal metabolism of prematurity before the present series and the one subsequently reported by Murlin. Most of the data in Table 1 appear in scattered publications incidental to other pieces of work. The results of these investigations are also recorded in the table.

A study of the figures of the heat production per unit of body surface in the table shows a wide variation in results. Rubner and Langstein's findings are much higher than those of the other investigators and presumably do not represent basal figures. The striking feature brought out by the results of the other investigators is the very low heat production of the premature infant.

The series reported below includes determinations of the basal metabolism of twenty-one premature infants. Some of the results have already been published in preliminary reports.[6]

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* Received for publication, April 19, 1923.

* From the Children's Medical Department, Massachusetts General Hospital.

1. Rubner and Langstein: Arch. f. Physiol., 1915, p. 39.

2. Weiss: Bull. de l'Acad. de méd., Paris **60**:458, Series 3, 1908.

3. Hasselbalch: Respirationsforsøg paa nyfødte Børn, Bibliot. f. Læger **8**:219, 1904.

4. Murlin and Marsh: Proc. Soc. Exper. Biol. & Med. **19**:431, 1922.

5. Benedict and Talbot: Pub. 233, Carnegie Institute, Washington.

6. Talbot, F. B., and Sisson, W. R.: Proc. Soc. Exper. Biol. & Med. **19**:309, 1922. Talbot, F. B.; Sisson, W. R.; Moriarty, Margaret, and Dalrymple, Alice: Basal Metabolism of Prematurity, II, Relation of Basal Metabolism to Caloric Intake and Weight Curve, Am. J. Dis. Child. **24**:95 (Aug.) 1922.

CLINICAL MATERIAL

The infants studied in this series, twenty-one in number, were patients at the Boston Lying-In Hospital and the Massachusetts General Hospital. The criteria used for establishing prematurity were weight, length, and general characteristics, such as facies, texture of the skin, undeveloped nails, cry, unstable temperature and history of expected birth. It was impossible in many instances to determine the exact date of the expected birth, but only such babies were selected for study who were at least from four to ten weeks premature. The actual stage of fetal life is difficult to estimate from either the physical examination or the mother's history. The estimates that have been made are based in most instances upon the obstetrician's prenatal examination and upon the date of the expected birth as given by the mother. In the majority of instances, the babies weighed less than 2 kilograms, were unable to nurse at the breast and had subnormal temperatures for the first few days of life. The low body temperatures were often raised with difficulty even though the babies were kept in a room at from 75 to 80 F., and received the usual care of premature cases. Hot water bottles were constantly kept in the bed and the infants wore suitable jackets.

Table 1.—*Previous Investigations on the Metabolism of Premature Infants*

Author	Age, Days	Sex*	Weight, Gm.	Height, Cm.	Respiratory Quotient	Heat Produced in 24 Hrs.			Remarks
						Total	Per Kilogram	Per Sq. M. $10\sqrt[3]{Wt.^2}$	
Hasselbalch [3]									
Case 5..............	2	♀	1,825	44	0.87	67.3	36.9	448	Died on third day
Case 15.............	5	♀	1,900	..	0.77	57.8	30.4	366	
Case 16.............	5	♀	1,900	..	0.81	63.9	33.6	404	
Weiss [2]									
Case 5..............	6	♂	1,530	..	0.70	82.8	54.0	606	
Case 8..............	6	♀	1,850	..	0.76	96.9	52.4	624	
Case 12.............	1	♂	1,950	..	0.81	93.1	47.7	579	
	3	..	1,800	..	0.82	96.9	53.8	636	
	5	..	1,800	..	0.83	92.1	50.0	591	
Benedict and Talbot [5]									
Case 24............	20½ hr.	♂	2,350	43	0.77	81.0	35.0	445	1 to 2 months premature; died subsequently of inanition
Rubner and Langstein [1]									
Case Koza..........	10	..	2,050	44	....	....	....	973	1+ month premature
Case Goerz.........	4	..	.....	45	....	....	....	1,032	1 month premature
	6	..	.....	..	....	....	....	956	
Fleming................	21	..	2,320	50	0.86	143.0	66.4	798	1 month premature

* In this column, ♀ indicates female; ♂, male.

The food consisted chiefly of human milk. At times, it was necessary to substitute modified cow's milk.

The clinical development of these babies can best be shown by reference to their weight curves, seven of which have already been published.[7] In Charts 1-14, inclusive, typical curves of the remaining infants of the series are shown. It will be noted that, in most instances, there was a period of stationary weight lasting for seven to ten days; but following this the development was generally satisfactory during the period of observation. The failure of these infants to gain during the first few days of life can be explained by frequent regurgitation and vomiting of food and mucus, and by the fact that human milk was unobtainable at the time. The weight curves show that in some instances there was no gain for from seven to ten days, but after this time most of the infants studied gained during the six to twelve weeks of observations. The characteristic weight curves are shown in Charts 1-14.

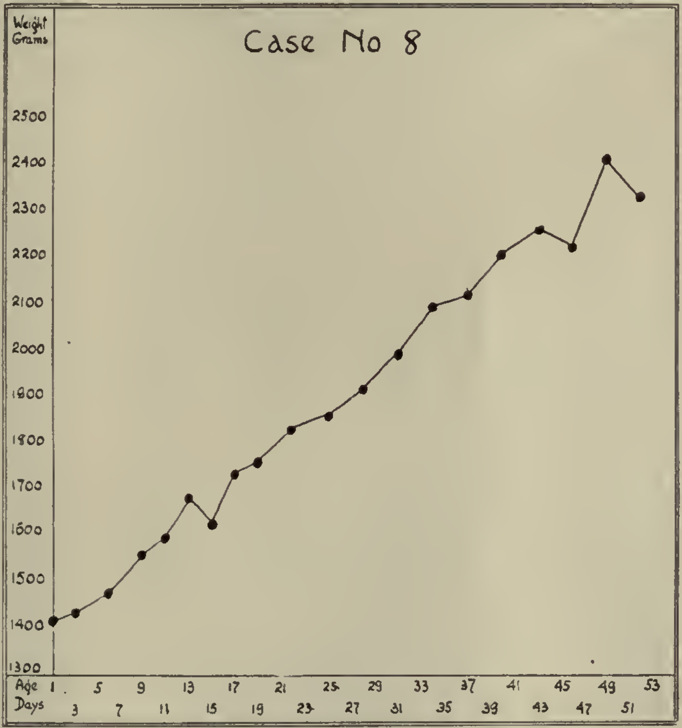

Chart 1.—Weight curve of premature infant.

The weight curve of Cases 1-7 inclusive may be found in an earlier report.[7] It was noted that in most instances the babies that had subnormal temperatures showed a slower initial gain than those that could easily be kept at normal body temperature, but eventually devolped satisfactorily. Complete physical examinations were made of all infants in this series, and abnormalities were recorded. The Wassermann reaction of the placental blood was negative in all instances except Case 8, in which the infant was congenitally syphilitic.

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[7] Talbot et al.: Footnote 6, second reference.

Table 2 gives the birth weight of these infants, with as accurate an estimation of their prematurity as was possible.

PROCEDURE

The baby was carried from the Boston Lying-In Hospital in a padded basket, surrounded by hot water bags. Before the laboratory was reached, the water in the bath surrounding the respiratory chamber was warmed to between 26 and 28 C., and the room itself was warmed to the same or a higher temperature. The infant was placed in the chamber wrapped in blankets, the cover lowered and, after the thermometers were inserted, the ventilation started. Great pains were taken to keep the room temperature as high as the temperature within the chamber, both for the accuracy of the measurements, and for the even maintenance of the infant's environment. The infant was fed immediately before observation was commenced.

Table 2.—*Birth Weight and Amount of Prematurity of Series of Premature Infants*

Case	Sex*	Estimated Prematurity, Days	Birth Weight, Gm.
1	♀	64	1,616
2†	♂	59	1,630
3	♂	59	
4†	♂	59	1,814
5	♀	59	1,814
6	♀	54	1,814
7	♀	46	1,654
8	♀	60	1,814
9	♀	14	1,899
10	♂	48	1,711
11	♂	68	1,191
12	♀	44	1,927
13	♂	43	1,814
14	♀	60	2,098
15†	♀	61	1,630
16	♀	61	1,630
17	♂	108	1,654
18	♂	60	1,810
19	♂	60 ?	1,361
20	♂	60	.....

* In this column, ♀ indicates female; ♂, male.
† Twins.

A preliminary period of from half to three quarters of an hour, which was always disregarded, passed before the actual determination. When the temperatures in the chamber became constant, the measurements were commenced, and the length of the period varied from seventy-five minutes to two hours, depending on the size of the infant and the amount of carbon dioxid eliminated. In no case could the

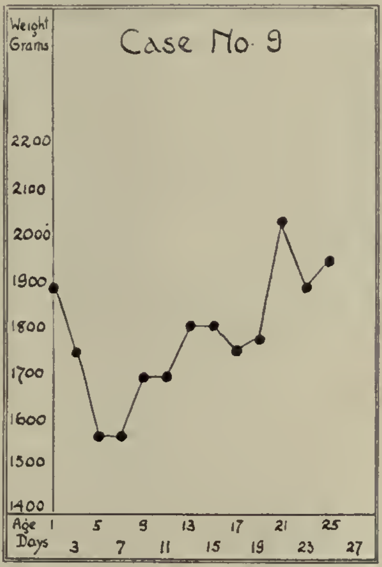

Chart 2.—Weight curve of premature infant.

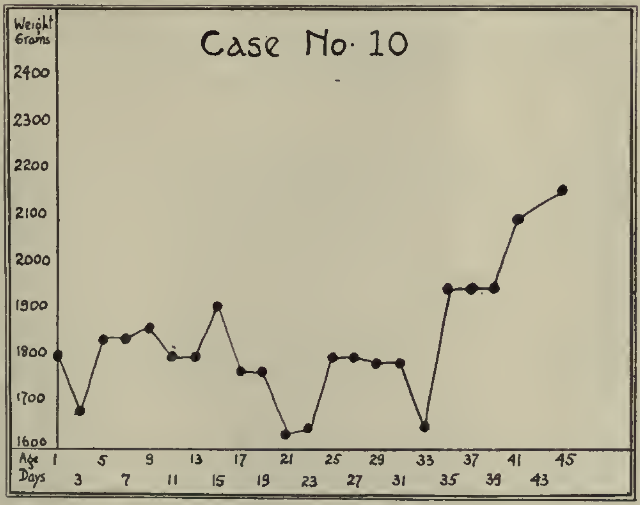

Chart 3.—Weight curve of premature infant.

period be continued longer than two hours without interfering with the feedings, which were given every three hours.

If the temperature of the respiratory chamber started to fall during the period, it could be raised again by means of two electric water heaters placed in the bath surrounding the chamber. It was invariably necessary to use the heater toward the close of the period to maintain the temperature of the chamber at the same level as at the beginning of the period. The experiment was ended in the manner previously described.[8] It was frequently impossible to record the pulse rate of these infants because they were so small that a stethoscope could not be attached to the chest. It was impractical to make electric cardiographic records. Consequently, the pulse rate has only been recorded in a few instances.

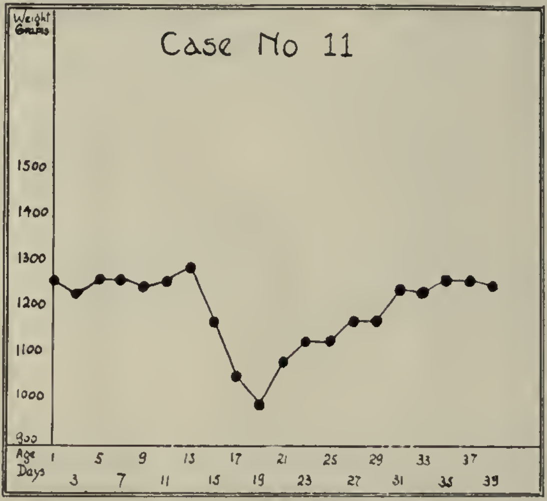

Chart 4.—Weight curve of premature infant.

In all cases, the body temperature of the infants was the same or slightly higher at the end of the period than before entry into the chamber.

Some of the data obtained during the first month of this investigation was subjected to severe criticism because of the small amounts of oxygen and carbon dioxid measured. As a result, the respiratory quotients of many observations were discarded. A number of alcohol checks were run to determine the smallest amount of carbon dioxid and oxygen that would give an accurate respiratory quotient, and the conclusion was reached that any amount appreciably less than 1 liter of

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[8] Benedict and Talbot: Pub. 201, Carnegie Institute, Washington.

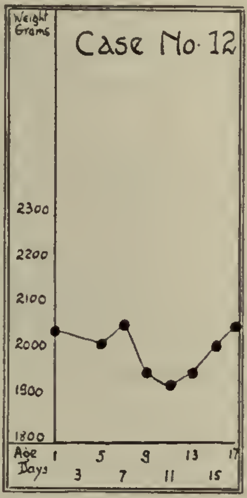

Chart 5.—Weight curve of premature infant.

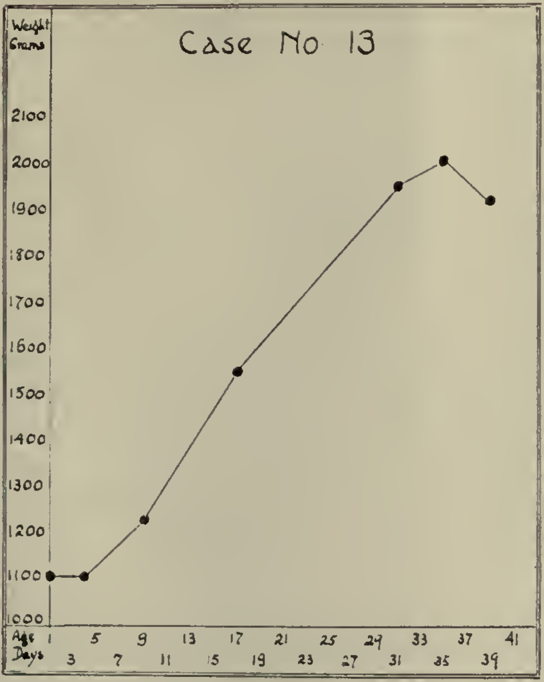

Chart 6.—Weight curve of premature infant.

oxygen and less than 1.4 grams carbon dioxid could not be depended on to give reliable respiratory quotients.[9] In those cases in which the measured amount of carbon dioxid and oxygen was lower than these minimum amounts, an average respiratory quotient was used in calculating the heat production from carbon dioxid. This quotient was obtained by averaging the quotients found in the infants that consumed enough oxygen and produced enough carbon dioxid to be above the selected minimum.

The average respiratory quotient of this series of premature infants was 0.96. This would seem to indicate that the principle source of their heat was carbohydrate. The respiratory quotient of the new-born infant determined in a large series of cases [5] was found to change during the first few days of life, falling quite rapidly after birth until the third day of life, when it reached its lowest, averaging 0.73. At this time, food influenced the quotient; it commenced to rise, and on the eighth day reached 0.80. During later infancy, it ran somewhat higher, and was occasionally above 0.90, even after the ingestion of food. In the adult, the postabsorptive quotient is 0.81.

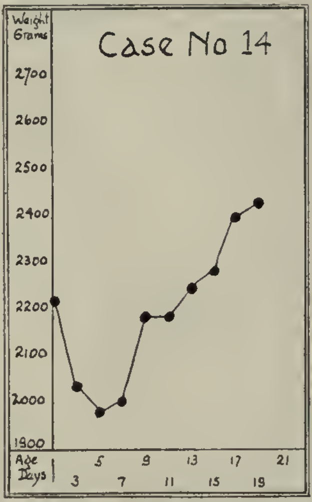

Chart 7.—Weight curve of premature infant.

Although the conclusion was reached that less than 1.4 gm. of carbon dioxid is not a large enough amount from which to estimate the respiratory quotient, it seems justifiable to use as small an amount as 1 gm. of measured carbon dioxid in estimating the heat production. During the early stages of the research, consideration was given to the probability of error when small amounts of carbon dioxid were measured. This was found to be less than was expected. It is shown in the figures of carbon dioxid excretion of premature twins and of two premature triplets measured separately and together, and also in cases in which several measurements were made on the same infant on the same or successive days. These are recorded in Table 3.

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[9] Unpublished data.

These figures show that even with very small amounts of carbon dioxid it is possible to obtain accurate results (A1 and A2). Table 4 also shows very close agreement. Even with the greater error in P2 and P3, the final table and charts show such uniformity in the general trend of the metabolism that the error which might be present in very small premature infants cannot have affected the results to any great degree.

Table 3.—*Carbon Dioxid Production of Twins, Separately and Together*

Case	Age, Days	Carbon Dioxid per Hour, Gm.
P2 and P3, together	18	1.93
P2, singly	16	1.31
P3, singly	16	0.98
		2.29
A1, singly	10	0.83
A2, singly	10	0.74
		1.57
A1 and A2, together	11	1.59

Table 4.—*Carbon Dioxid Production of Premature Infants on the Same Day or on Successive Days*

Case	Date	Carbon Dioxid Production per Hour, Gm.
18 (Table 5)	3/22/20	1.43
	3/23/20	1.46
	3/24/20	1.43
8 (Table 5)	1/25/22	1.11
	1/26/22	1.11
	1/27/22, a. m.	1.28
	1/27/22, p. m.	1.30
	2/ 7/22, a. m.	1.32
	2/ 7/22, noon	1.39
	2/ 7/22, p. m.	1.37

Table 5 gives the basal metabolism findings in a series of the twenty-one premature infants studied.

COMMENT

The usual custom of charting the values in relation, first to age, then to body weight and finally to body surface has been followed. Since the work of Benedict and Talbot[10] has shown that there is little or no sex differentiation below the weight of 11 kg., these cases have not been charted by sex.

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[10] Benedict and Talbot: Pub. 302, Carnegie Institute, Washington.

Each point on the charts represents a separate metabolism determination, but not a different subject in all cases. In some instances, determinations were made on the same child at different ages. In Case 6, the metabolism was determined nine times at different ages, covering in all a period of three months. The metabolism in Case 8 was determined on three successive days, on the last of which observations were made in the morning and the afternoon. Reference to the table shows how closely these figures correspond, and speak again for the accuracy of the results. When the metabolism was determined on successive days, it was averaged and placed on the chart as a single dot.

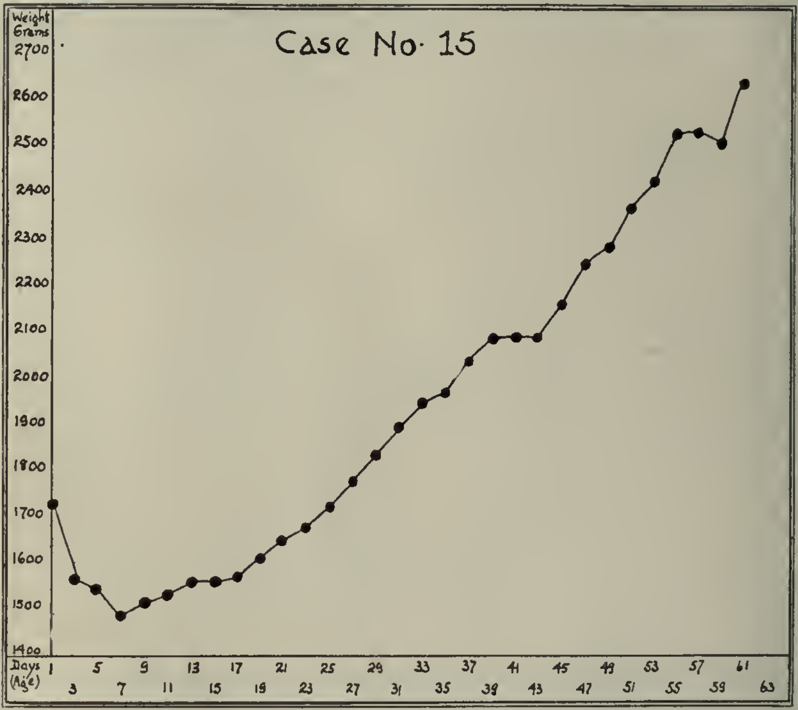

Chart 8.—Weight curve of premature infant.

GENERAL TREND OF THE METABOLISM WITH INCREASING AGE

The total calories for twenty-four hours, as referred to age, have been outlined in Chart 15, which shows that there is a gradually increasing heat production with increasing age. The lowest heat production was found in the first ten days of life (Cases 1, 3, 4, 11).

TABLE 5.—*Basal Metabolism Findings in a Series of Twenty-One Premature Infants*

Case	Age, Days	Date	Weight, Kg.	Height, Cm.	Sitting Height, Cm.	Length of Period, Min.	Oxygen Measured,* Gm.	Carbon Dioxid Measured, Gm.	Carbon Dioxid per Hour, Gm.	Respiratory Quotient	Total Calories	Calories per Kilogram	Calories per Square Meter		Activity	Pulse Rate	Temperature of Baby (Fahrenheit)		Temperature of Box (Centigrade)	
													DuBois	Benedict and Talbot			Before	After	Before	After
1	4	2/14/22	1.418	....	....	97	.....	1.17	0.72	0.96†	46.0	32.5	.....	361.1	I	...	98.1	.....	28.23	28.44
	6	2/16/22	1.432	42.0	28.0	92	.....	1.35	0.88	0.96†	56.0	39.2	462.8	436.8	I	...	98.8	.....	28.15	28.31
2	16	1/31/22	1.644	46.0	28.0	92½	0.972	2.02	1.31	1.06	80.8	49.1	535.0	580.0	I	...	99.0	99.0	28.47	28.60
	33	2/17/22	2.155	47.0	30.5	96	1.770	3.39	2.19	0.98	132.8	61.6	785.0	795.2	I	...	98.9	.....	29.99	29.75
3	16	1/31/22	1.474	42.5	26.5	96½	0.964	1.58	0.98	0.83	70.0	47.5	485.8	540.0	I	...	98.8	.....	29.78	28.44
	34	2/18/22	1.843	42.5	29.1	97	1.460	3.00	1.86	1.05	114.4	62.1	747.8	761.1	I	...	99.0	.....	29.77	30.27
4	10	2/ 1/22	1.757	42.5	28.0	109	.....	1.50	0.83	0.96†	52.5	29.9	394.8	360.7	I	...	99.0	.....	26.47	26.54
	24	2/15/22	1.673	45.5	28.5	94½	.....	2.43	1.54	0.96†	98.1	58.7	663.0	696.0	I	...	98.8	.....	28.52	28.40
5	10	2/ 1/22	1.644	43.0	27.0	101½	.....	1.25	0.74	0.96†	47.0	28.6	330.9	334.0	I	...	98.1	98.2	29.93	29.87
	25	2/16/22	1.970	46.8	29.2	99¼	1.280	2.41	1.46	0.96	92.7	47.0	648.0	583.8	I	...	98.8	.....	28.02	28.79
6	9	11/10/21	1.616	....	....	53	.....	1.10	1.25	0.96†	79.2	49.0	.....	569.4	I+	156	98.8	99.2	29.05	28.76
	11	11/12/21	1.715	....	....	72	.....	1.29	1.08	0.96†	68.4	39.9	.....	472.5	I	146	98.8	100.0	30.98	30.28
	15	11/16/21	1.772	43.8	29.0	87½	.....	1.42	0.97	0.96†	61.9	35.0	430.1	418.7	I	...	99.0	99.3	27.10	26.83
	30	12/ 1/21	1.814	....	....	65½	.....	1.21	1.11	0.96†	70.5	38.9	.....	469.3	I+	...	99.0	98.8	29.24	28.89
	45	12/15/21	2.098	....	....	86½	1.050	2.39	1.66	0.96†	105.4	50.3	.....	637.0	I	127	98.8	99.8	33.52	32.24
	50	12/20/21	2.183	....	....	66½	1.110	2.14	1.93	0.98	120.9	55.4	.....	711.3	I	...	99.0	.....	30.66	30.46
	58	12/28/21	2.381	....	....	49½	1.160	2.04	2.47	0.90	165.3	69.4	.....	917.7	I	110	99.4	98.0	31.25	31.00
	64	1/ 5/22	2.495	47.0	31.8	53½	.....	1.93	2.16	0.96†	137.7	55.2	769.1	740.9	I	...	98.6	.....	28.99	28.75
	97	2/ 8/22	3.019	53.0	34.0	75	2.060	3.84	3.07	0.95	196.9	65.2	911.7	933.5	I	...	.....	.....	23.90	23.83
7	14	11/29/21	1.559	....	....	69	.....	1.34	1.17	0.96†	75.8	47.5	.....	545.7	I	...	100.4	99.5	30.43	30.16
	23	12/ 8/21	1.616	47.0	29.5	91½	.....	1.63	1.07	0.96†	68.0	42.1	539.5	488.8	I	...	99.2	99.3	31.00	30.28
	45	12/30/21	1.942	....	....	65	.....	1.41	1.30	0.96†	82.8	42.6	.....	526.5	I	151	98.6	.....	31.35	29.72
	65	1/10/22	2.467	48.8	35.4	89½	1.620	3.30	2.21	1.04	136.4	55.3	762.0	739.7	I	...	98.6	99.3	29.70	29.98
8	15	1/25/22	1.474	....	....	80	.....	1.48	1.11	0.96†	70.6	47.9	.....	539.7	I	...	100.0	99.6	28.81	29.11
	16	1/26/22	1.559	....	....	69½	.....	1.28	1.11	0.96†	70.3	45.1	.....	513.4	I	...	99.2	100.2	29.39	28.29
	17	1/27/22	1.559	....	....	68	.....	1.45	1.28	0.96†	81.4	52.2	.....	599.2	I	...	98.0	98.2	26.92	26.62
		1/27 p.m.	1.559	....	....	92	1.040	2.09	1.30	0.98	81.7	52.4	.....	601.4	I	...	99.6	99.8	26.91	27.82
		2/ 7/22	1.814	45.0	30.5	146	1.630	3.20	1.32	1.00	81.1	44.7	523.1	539.7	I	152	99.0	98.6	28.43	29.24
		2/ 7/22	.....	....	....	164	2.060	3.80	1.39	0.94	89.9	49.6	580.1	598.6	I	152	98.6	98.8	28.76	28.34
		2/ 7/22	.....	....	....	184	2.640	4.19	1.37	0.81	99.2	54.7	640.0	660.3	I	152	98.8	98.6	28.05	28.41
9	11	11/23/22	1.701	43.5	28.5	92	0.900	1.71	1.12	0.88	75.9	44.6	583.8	520.9	I	...	98.2	99.4	26.89	26.68
	23	12/ 5/22	1.928	44.5	29.1	87	1.390	2.63	1.81	0.96	115.4	59.8	769.0	737.3	I	...	98.8	99.4	28.23	27.57
10	6	2/ 6/22	1.729	43.0	26.2	91	.....	1.94	1.28	0.96†	81.4	47.1	707.4	564.8	I	...	99.4	100.4	27.79	27.44
	9	2/ 9/22	1.744	....	....	95	1.110	2.07	1.31	0.95	83.8	48.1	.....	578.4	I	...	99.6	99.6	28.70	28.37
11	3	6/ 3/21	1.191	....	....	75	.....	0.75	0.60	0.96†	38.2	32.0	360.0	339.6	I	...	99.4	98.6	24.47	24.15
	36	7/ 6/21	1.191	38.0	....	54	.....	0.82	0.91	0.96†	57.9	48.7	508.3	515.7	I	...	.....	.....	29.68	28.60
12	7	5/20/21	1.864	....	....	69	0.990	1.44	1.25	0.74	97.7	52.4	.....	638.8	I	...	98.8	.....	28.48	26.98
	19	6/ 1/21	2.055	....	....	67	.....	1.66	1.49	0.96†	94.5	46.0	.....	579.1	I	...	100.0	.....	25.06	24.65
13	48	2/15/21	1.559	40.5	....	76½	0.900	1.70	1.33	0.97	84.1	54.0	623.2	625.7	I	153	100.2	.....	30.54	29.44
14	12	4/11/21	2.070	....	....	65	.....	1.47	1.36	0.96	86.3	41.7	.....	526.1	I	140	99.6	.....	30.09	29.66
15	50	4/ 7/21	2.293	45.5	....	56½	1.230	2.32	2.46	0.96	156.7	68.2	885.3	891.4	I+	153	99.6	100.2	29.89	29.69
16	42	3/30/21	.....	....	....	48	1.239	2.31	2.89	0.95	185.1‡	81.6‡	954.1‡	106.2	II+	185	98.8	99.4	32.10	31.30
17	26	4/ 1/21	.....	....	....	49	.....	2.07	2.53	0.96	161.2‡	83.6‡	989.0‡	104.0	II+	151+	99.4	100.2	30.60	30.24
18	21	3/22/20	1.915	46.1	....	89	.....	2.12	1.43	....	90.9	47.5	.....	539.5	I	...	100.4	98.0	29.19	27.86
		3/23/20	1.895	....	....	61½	.....	1.50	1.46	....	93.1	49.1	.....	607.8	I	...	99.4	96.4	21.33	21.57
		3/24/20	1.875	....	....	67	.....	1.60	1.43	0.96†	91.1	48.6	.....	599.3	I	...	98.6	97.4	27.01	26.72
		3/26/20	2.078	....	....	52½	.....	1.35	1.54	....	98.1	47.2	.....	602.6	I	...	98.8	98.2	23.29	23.13
19	27	12/14/20	1.460	44.5	....	86	.....	1.67	1.17	0.96†	74.1	50.8	.....	575.8	I	...	99.0	101.0	33.86	32.65
	34	12/21/20	1.616	....	....	70½	.....	1.46	1.24	0.96†	79.0	48.9	.....	573.9	I	...	98.8	99.8	31.59	30.22
	50	1/ 6/21	1.014	....	....	45	.....	1.57	2.09	0.96†	133.1	69.6	.....	863.7	I	164	100.1	100.0	31.19	30.20
20	90	1/25/22	2.622	....	....	61	.....	1.89	1.86	0.96†	118.2	45.1	.....	622.1	I	...	98.6	99.2	29.87	29.00
21	10	12/19/21	1.871	....	....	53	.....	1.28	1.45	0.96†	92.2	48.3	.....	607.0	I	122	.....	.....	27.70	27.08

* Where no figures for oxygen are given, the amount measured was less than 1 liter.

† Assumed average quotient (see text).

‡ Not basal. The infant cried about seven minutes of fifty-minute period.

There did not seem to be any relation between the level of the heat production and the prognosis of these infants because some of them gained weight and strength rapidly, and others did not gain at first but did later. In some cases, even with only a slow gain in weight, the heat production increased quite rapidly with age. In Case 11, the heat production increased slowly, 37 calories on the fourth day and 57 on the thirty-sixth day, the weight remaining stationary during this time. The infant died at about 2 months. This single case suggests that a low metabolism which does not increase with age indicates inanition and a poor prognosis. On the other hand, a metabolism that increases with age, as shown by the other cases, does not necessarily mean a good prognosis, because many factors other than the power to produce heat influence the mortality of premature infants. None of the other infants died while being followed by us. The infants in Case 7 died of unknown causes two months after it passed from our supervision.

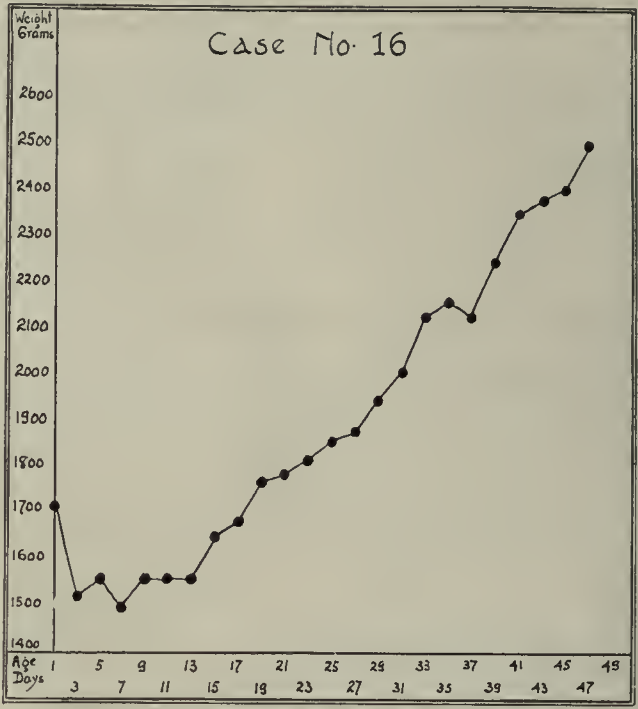

Chart 9.—Weight curve of premature infant.

The relation of the total heat production of premature infants to that of normal infants of the same age is shown in Chart 16, which

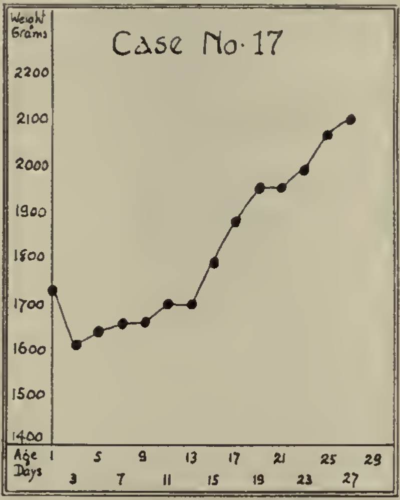

Chart 10.—Weight curve of premature infant.

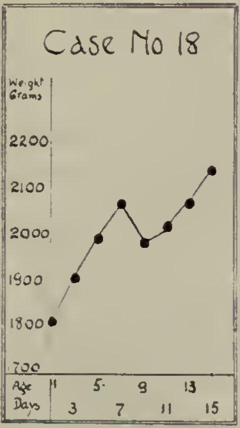

Chart 11.—Weight curve of premature infant.

shows the total heat production for twenty-four hours of normal infants [5] in a solid black line. Below it is the curve for premature infants, indicated by a dotted line. This shows that the total heat production for twenty-four hours of a premature infant is considerably lower and tends to run parallel with that of the normal, full-term infant.

Although the metabolism of premature infants is plotted against their age after birth, it does not represent their physiologic age because the expected birth should be 279 days after the last menstrual period. Even this method of reckoning may be inaccurate. The impossibility of obtaining accurate data concerning the age detracts from the value of all the curves in which age plays a part. The question of what is the true age of a premature infant is hard to answer. It can be figured from birth onward, or from the date of the expected birth; in the latter case, the days preceding the expected birth should be indicated as minus days.

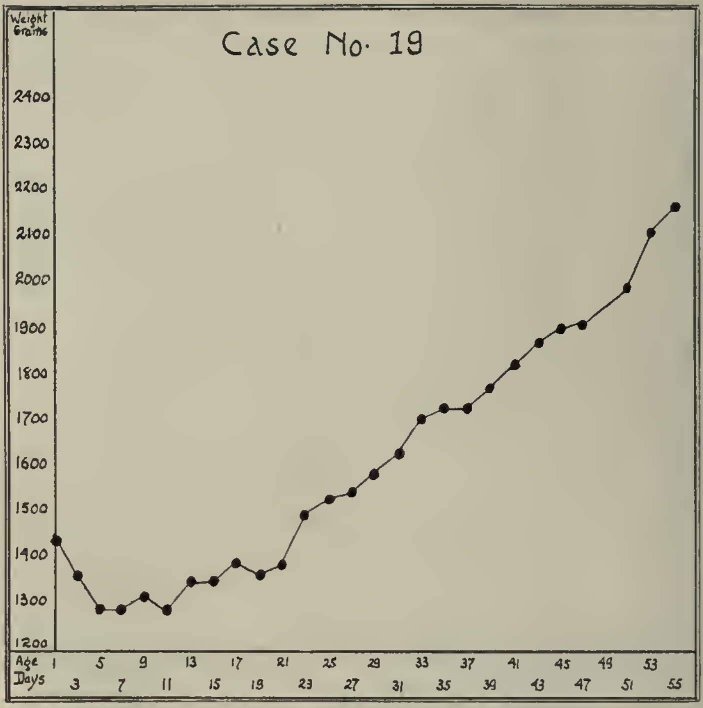

Chart 12.—Weight curve of premature infant.

The general trend of the metabolism in relation to either the actual birth or the expected birth is lower than, and parallel to, that of normal

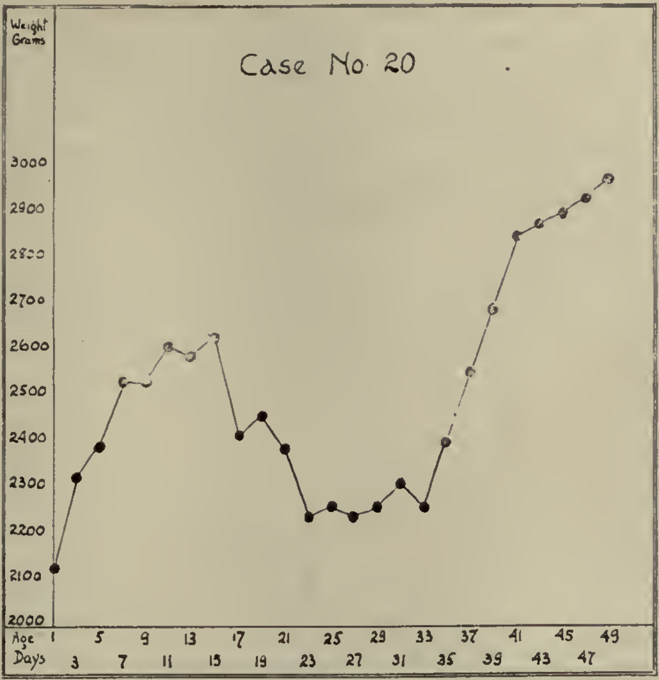

Chart 13.—Weight curve of premature infant.

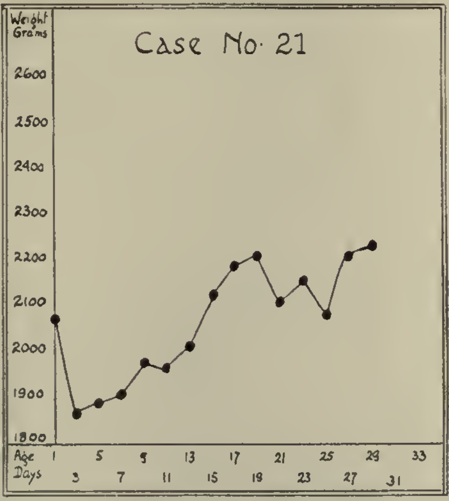

Chart 14.—Weight curve of premature infant.

full-term infants. The curves are closer together when plotted for expected age than for actual age. The very small amount of heat produced by some of these infants is striking. It is consistent with the clinical fact that it is difficult to keep these babies warm, and that constant care and the application of external heat are necessary in order to maintain the body heat. Sudden death in the premature infant during the early days after birth is not at all uncommon, and it would seem that infants with the lowest basal metabolism require the most care to maintain life.

In a few instances, we were able to obtain sufficiently accurate histories to warrant plotting the heat production in relation to the expected birth of the infant. This has been done in Chart 17. The days before the expected birth have been indicated as minus days. The general trend of the metabolism is upward, rising with age in a way similar to the curve plotted in Chart 15, which, with Chart 17, shows an increasing heat production with increasing age, whether the days are counted from the actual birth or from the expected birth. The curve of the metabolism of the premature infant is much closer to the normal after the expected birthday than after the actual birthday. The trend in both instances is similar, and shows that, with increasing age and

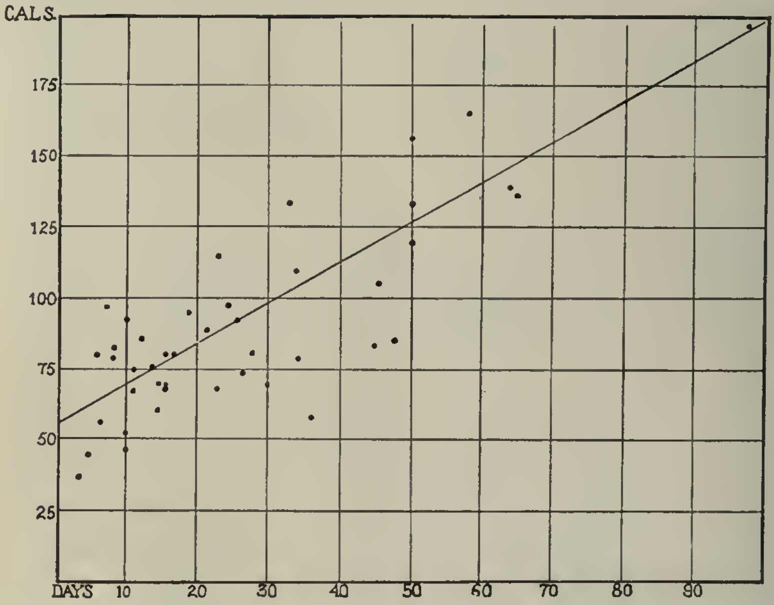

Chart 15.—Basal heat production of premature infants for twenty-four hours, as referred to age.

weight, there is an increase in the total heat production. This apparently means that the premature infant, even in the best surroundings, does not develop as rapidly as it would had it reached full term. It is probable that this handicap persists for several months after birth. An example of a premature infant with malnutrition is to be found in Case J. V.,[9] who had a much lower total metabolism at the age of 8 months than normal infants of the same age. The question still remains to be solved as to how long it takes a prematurely born infant to reach the size and development of the full-term infant. Probably the earliest age at which a 4 or 5 pound (1.81 to 2.27 kg.) premature infant catches up with a normal infant is from 3 to 4 months, and the

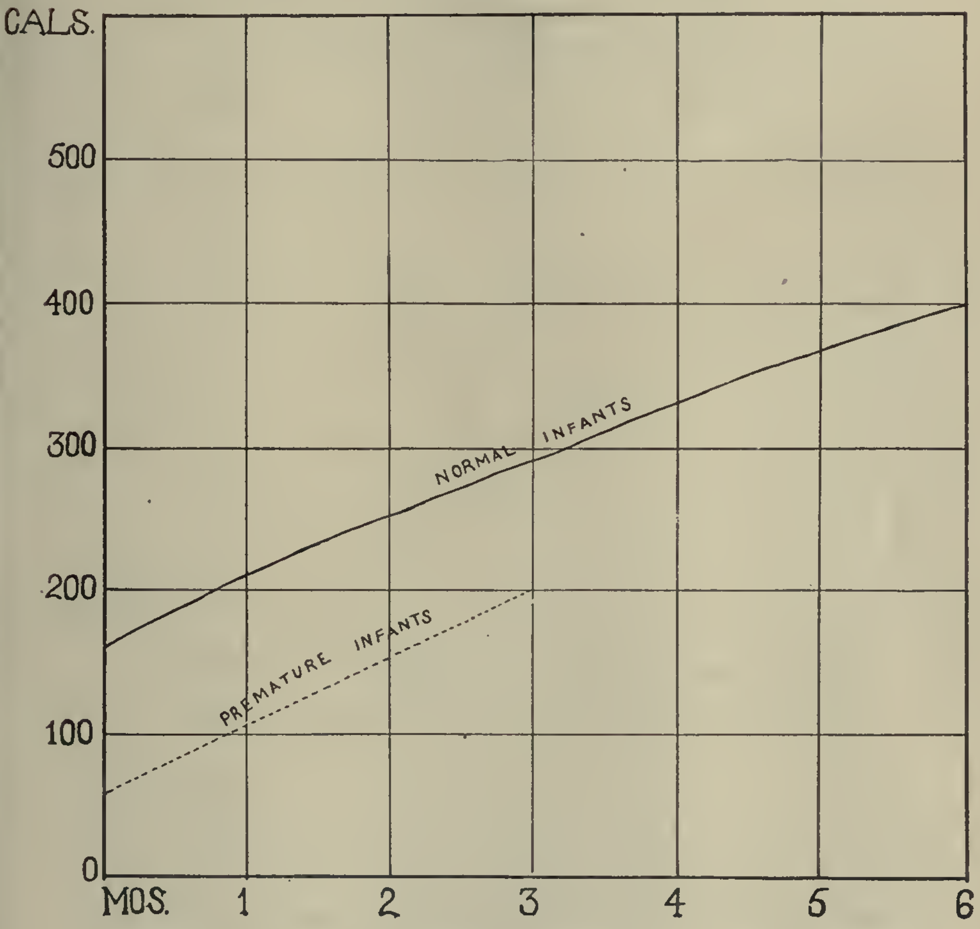

Chart 16.—Total heat production, for twenty-four hours, of normal and premature infants, as referred to age.

smaller the infant, the longer it takes. The relatively greater growth of the premature infant necessitates a larger proportional food intake to supply the material for growth. This, in turn, puts more strain on the organs of digestion and assimilation, which must function normally to obtain successful results.

It has been shown that the total calories produced by normal infants and children, boys especially, can be predicted for a given weight with a considerable degree of accuracy.[11] The heat production of the premature infant has been plotted against body weight in Chart 18, which shows also the curve of the heat production of normal, full-term infants. The heavy babies have a greater heat production than the lighter ones.

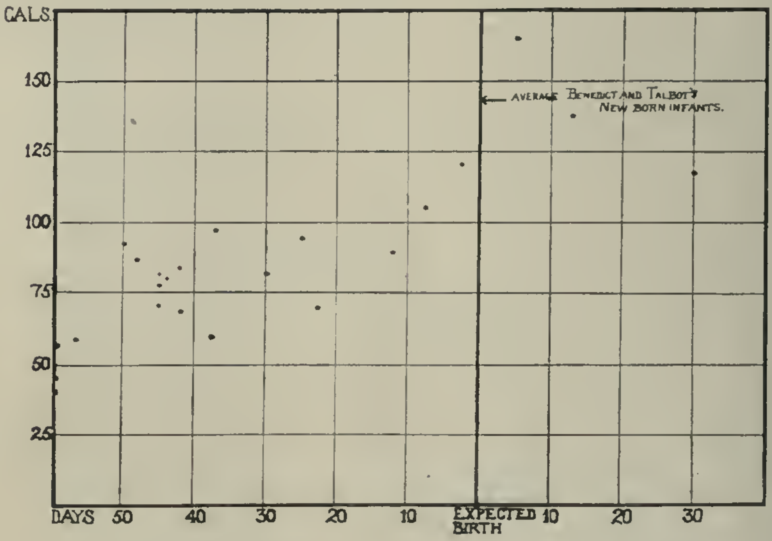

Chart 17.—Total calories in relation to expected birth.

The records of most of the infants weighing more than 1.8 kg. would place them above the curve.[12] Records of the infants weighing between 1.8 and 1.2 kg. would place them in about equal numbers on either side of this line, if it were projected backward. The total heat production plotted against weight appears to be higher in the premature than in the normal infant. This is indicated only in the heavier infants, weighing 2.5 kg. or more, which can be compared with normal infants. This relationship is also found in infants with malnutrition,[13] whether premature or not, and there is good reason to believe that the explanation is the same in both instances. The relatively high metabolism of infants with malnutrition is believed to be due to the absence of the diluting factor of inactive tissue, which is represented especially by body fat, and to the presence of a greater proportional amount of active tissue. Whether the lowest portion of the field represents the basal metabolism of late fetal life, and whether projection of the curve backward will predict the metabolism of the fetus from the time of inception to its birth, opens a fascinating field of conjecture.

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[11] Benedict: Proc. Nat. Acad. Sc. **6**:9, 1920.

[12] Benedict and Talbot: Pub. 302, Carnegie Institute, Washington.

[13] Talbot, F. B.: Severe Infantile Malnutrition; Energy Metabolism with Report of a New Series of Cases, Am. J. Dis. Child. **22**:358 (Oct.) 1921.

In plotting the total metabolism against height, the dots fell so widely apart that they did not give a characteristic picture. It was concluded that, as in the normal infant, the heat production of the premature infant was not proportional to its height.

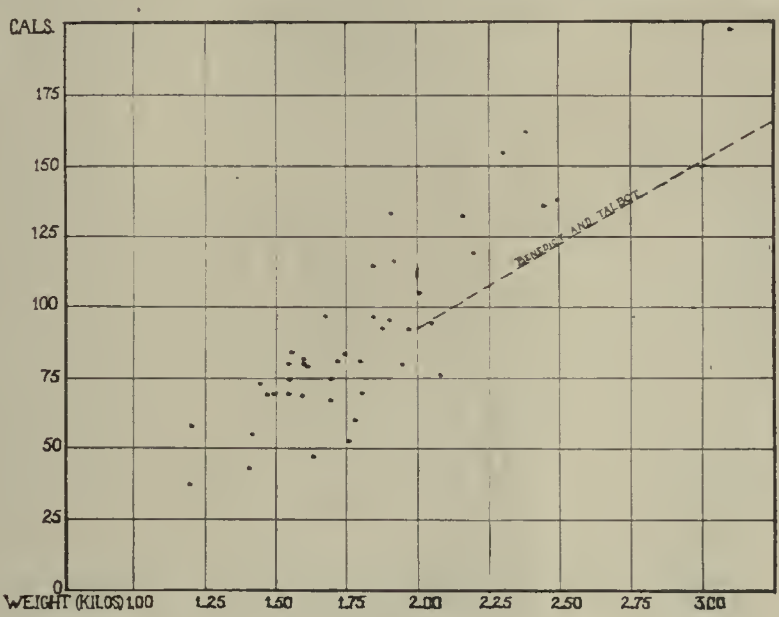

Chart 18.—Basal heat production for twenty-four hours, as referred to body weight.

Recently, considerable interest has been evinced in the relation of the stem length to the caloric needs of children. In a few instances, measurements were taken of the stem length of the infants. This measurement often was made with great difficulty, and there was present a possible error of 1 cm. In Chart 19, the total calories per twenty-four hours are plotted against the stem length. A general increase in the heat production with increasing stem length is shown. The differences are great; for example, there is a difference of 100 per cent. in the heat production of infants with a stem length of 29 cm.

When the metabolism is plotted against the total length of the body, the differences are even greater. It is obvious, therefore, that stem length, in these few observations, does not give a measurement from which to predict the basal metabolism of premature infants, because such prediction can be of real importance only when there is a maximum deviation from the average of 6 per cent. or less.

HEAT PRODUCTION PER KILOGRAM OF BODY WEIGHT

The calories per kilogram plotted against age show distribution very similar to that of normal infants. The most striking feature of this picture is that, in the early days of life, the metabolism tends to run much lower than the normal, and after forty days to be higher. Normal infants never have a heat production of less than 41 calories per kilogram, while in eight instances premature infants produced less than this. This seems to indicate that the fire burns very low during the early days of their life; a conclusion quite consistent with clinical experience.

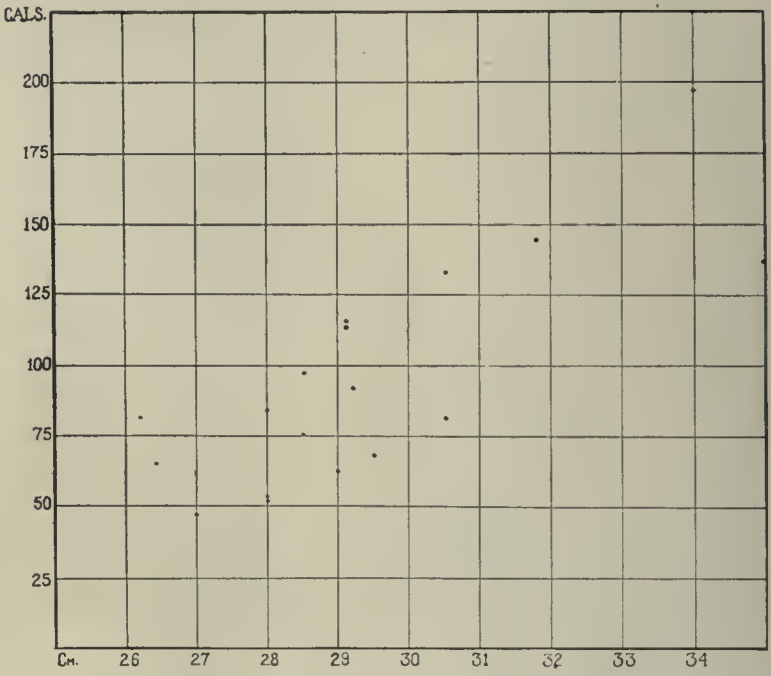

Chart 19.—Total calories, as referred to "sitting height."

The question arises as to whether the low metabolism is due to the age of the premature infant, or to its small weight. The heat production per kilogram of body weight is of value in showing the influence of both age and weight (Chart 20 and 21) on the intensity of the metabolism. Since many factors complicate the interpretation of these figures, only general tendencies may be indicated.

The Benedict and Talbot curve for normal infants is plotted in dashes. This shows a general tendency for the heat production of premature infants to be higher than that of normal infants of the same weight (Chart 21).

The heavier the infant, the higher the dots are above the average line of normal infants; the majority of those indicated by dots falling below the line weighed less than 2 kg. This is in accordance with the variations seen on the age charts. The four lowest dots, although representing the metabolism of very small infants, also represent that of very young infants in the first days of life. Clinically, these infants are very weak and require the greatest attention to maintain their body temperature, so it seems probable that this extremely low metabolism is connected with their age rather than with their weight. This tendency may also be found in the normal new-born infants[8] whose lowest heat production, 32 calories per kilogram, was found on the first day of life, in infants of different weights, respectively 3.3, 3.9 and 4.1 kilograms. It seems probable, therefore, that the metabolism dur-

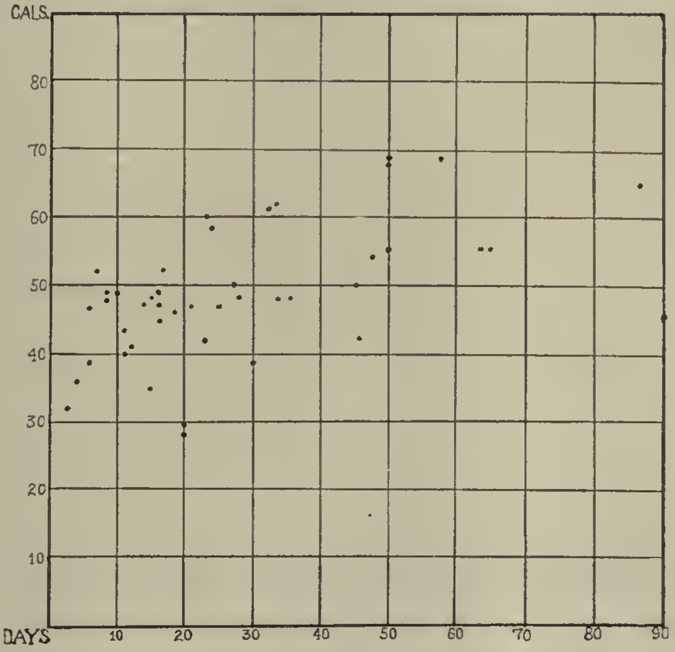

Chart 20.—Calories per kilogram, as referred to age.

ing the first days of life, in premature as well as in normal infants, differs from their metabolism after they have become adapted to their surroundings. That the metabolism of the premature should be low longer than that of the normal infant is quite in accord with clinical observations, because the former has to be guarded against the slightest exposure for weeks and the latter only for days.

The tendency of the metabolism of the other premature infants to fall above the average of the normal infant seems to give further evidence to the explanation that their bodies are composed principally of active tissue and are deficient in inactive tissues, such as fat.

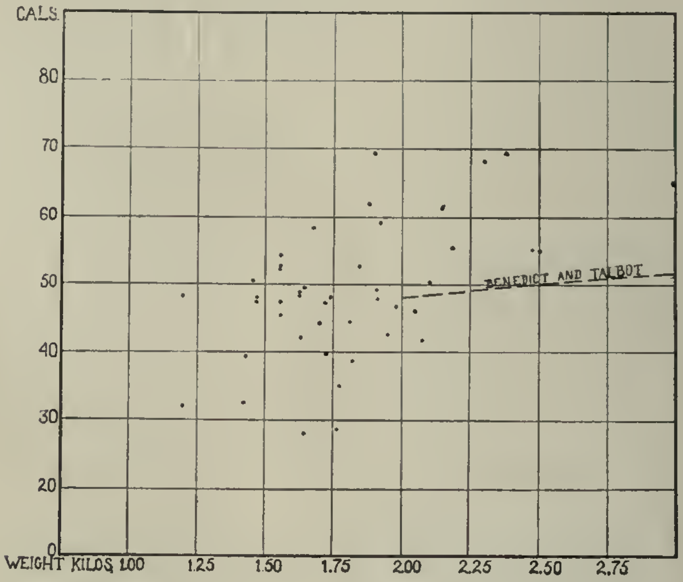

Chart 21.—Calories per kilogram of body weight, as referred to total weight.

HEAT PRODUCTION PER SQUARE METER OF BODY SURFACE

To determine the influence of body surface on the basal metabolism, careful measurements of as many premature infants as possible were taken according to the Du Bois linear measurements. It was found that, with the formula $10.0\sqrt[3]{Wt_2}$ boys and $10.1\sqrt[3]{Wt_2}$ girls recommended by Benedict and Talbot,[12] the surface calculated, by mathematical analysis,[14] approximated more closely the surface obtained by the Du Bois linear formula than by any other method. This factor has consequently been used in Charts 22 and 23, in which the Du Bois measurements were not taken both because of the accuracy of the formula and because the results are comparable with other standard curves of normal infants.

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[14] Unpublished data.

These two charts show that with increasing age and with increasing weight, there is an increasing heat production.

Chart 21 shows again the surprisingly low heat production in the early days of life that was indicated in the previous charts. It was first thought by Rubner that the heat production of all animals was 1,000 calories per square meter of body surface. Later, Schlossmann and Murschhauser[15] showed that, in quiet, healthy infants, the heat production per square meter of body surface might be as low as 866 calories. Benedict and Talbot[8] found that, in new-born infants, it was as low as 612 calories, and that the heat production per unit of surface increased with increasing age up to 18 months. The extraordinarily low findings of 330 and 360 calories in these premature infants are very striking. Hasselbalch's[3] results were likewise low, in one case 366 calories and another 404. These were all in very young infants whose heat regulation was presumably still unstable. The relation between body weight and heat production per unit of surface was not so consistent. The weight of the four infants that had the lowest heat production varied

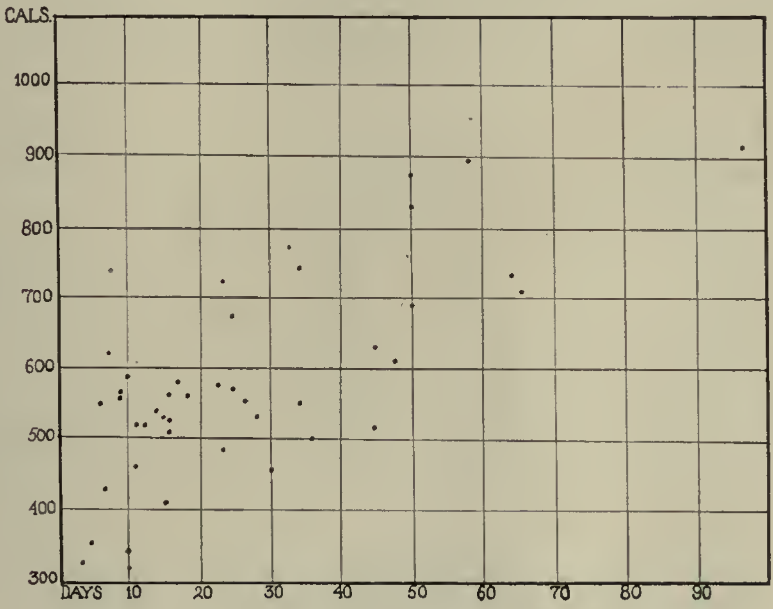

Chart 22.—Calories per square meter, as referred to age.

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[15] Schlossmann and Murschhauser: Biochem. Ztschr. **14**:369, 1908.

from 1.2 to 1.75 kg.; while the heat production of infants whose weights were between 1.77 and 1.93 kg. varied from 410 to 834 calories. It confirms again the previous charts, which indicate that in very young infants a low metabolism is more often connected with age than with weight. In general, however, the greater the body weight, the higher the heat production. In Chart 23, the Benedict and Talbot curve,[12] plotted in dashes, shows that, in premature infants weighing less than 1.8 kg., there is a tendency for the heat production to be lower than the expected heat production of a normal infant; whereas, in these infants weighing more than 2.1 kg., the heat production was higher than that expected in normal infants.

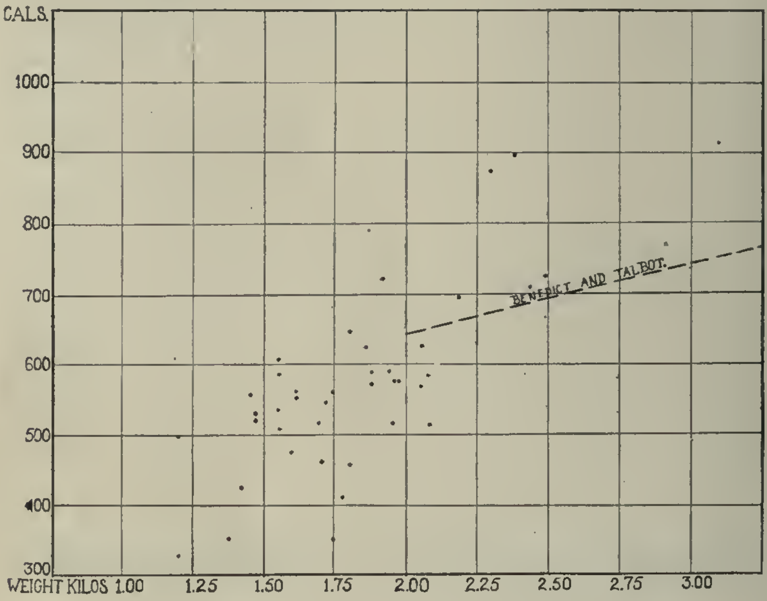

Chart 23.—Calories per square meter, as referred to weight.

The heat production per unit of surface area of the premature infant is, in the majority of instances, less than that of the normal infant. The reason that there is not excessive heat loss in these infants is that the surrounding temperature is kept high enough to prevent this. If a premature infant were exposed to cold, there would presumably result a rapid loss of heat from the body, but not a compensatory increase in heat formation, because it is incapable of forming more heat in early life. As a consequence, the loss of heat from the body is greater than the amount of heat formed, and the body temperature becomes subnormal. If this condition is allowed to continue over any length of time, death nearly always results.

BODY TEMPERATURE AND ITS RELATION TO THE BASAL METABOLISM

The premature infant, especially in the early days and weeks of life, is kept warm with difficulty, and any undue exposure results in a rapid loss of heat from the body, which is not replaced as it is in normal infants by heat formed from muscular exercise. The babies have not enough strength to exercise, and instead of crying or shivering as does the healthy full-term infant, they lie quiet, and extra heat lost from the body is not replaced. In this respect, the premature infant belongs physiologically to the same class as the cold-blooded animal. One would expect, if this were so, that there would be a higher production of heat when the temperature was elevated than when it was low. Case 18, however, did not show any change in the metabolism on each of three successive days when the body temperature varied.

TABLE 6.—*Heat Production of Case 18, with Varying Body Temperature*

Date	Total Calories per 24 Hours	Body Temperature (Fahrenheit)		Temperature of Chamber (Centigrade)	
		Before Period	After Period	Beginning	End
3/22/20................	90.9	100.4	98.0	29.19	27.86
3/23/20....	93.1	99.4	96.4	21.33	21.57
3/24/20................	91.1	98.6	97.4	27.01	26.72

There was no change in the metabolism of any infants in this series that could be attributed to change in the temperature of the body or its surroundings. It seems probable that if the temperature were allowed to remain subnormal for any length of time, the metabolism would also have fallen, just as it does in the coldblooded animal.

THE EFFECT OF EXERCISE ON THE METABOLISM OF PREMATURE INFANTS

It was shown in an earlier publication [8] that, on the average, a maximum increase in metabolism of 65 per cent. may result in the new-born infant from vigorous kicking and crying, and that, up to the age of 6 months, the average increase due to activity may be as high as 40 per cent.

The prematurely born infant is much less vigorous than the infant born at term; the smaller and more premature an infant is, the weaker it is. Cases 16 and 17, given as examples of activity, moved very frequently, but not vigorously, and there was some discussion as to whether their activity should have been recorded as II or III. It was finally recorded as II +, which is a fair estimation when comparison is made with that of normal infants; but when the fact that they were premature infants is taken into consideration, the activities might have been recorded as IV or V. The fact that the activity is relative makes it difficult to estimate it for a subject that does not conform in other ways with a normal infant. Since the premature infant usually remains very quiet a greater part of the twenty-four hours, what seems to be slight activity is of much greater importance than at any other period of life because it presumably takes more effort to make a slight exertion. Fortunately, it is possible to compare the metabolism of the infant in Case 16 who was moving, with that of her twin sister (Case 15), who was absolutely quiet. This shows that the basal metabolism of the active twin was 11 per cent. higher than that of the quiet twin.

The infant in Case 17 can also be compared with another premature infant of the same weight and approximately the same age.

Table 7.—*Comparison of Metabolism of Twin Sisters of Same Weight Showing Effect of Activity*

Case	Weight, Kg.	Total Calories	Metabolism per Kg.	Metabolism per Sq. M.	Pulse	Activity
15 (Malnutrition I)............	2.29	156.7	68.0	891	153	1
16 (Malnutrition II)...........	2.26	185.1	81.6	1,062	185	11+

Table 8.—*Comparison of Metabolism of Infants of Same Weight Showing Effect of Activity*

Case	Weight, Kg.	Total Calories	Metabolism per Kg.	Metabolism per Sq. M.	Pulse	Activity
9...............................	1.928	115.4	59.8	737	...	I
17..............................	1.928	161.2	83.6	1,040	151+	II+
22 (16 days)....................	2.098	185.0	88.2	1,117	...	Crying

The metabolism of the active infant (Case 17) is 40 per cent. higher than that in the basal case (Case 9). Since the recorded activities in Cases 16 and 17 were to all intents and purposes identical, the results show how much more difficult it is to estimate the amount of activity in a premature than in a normal infant. The effect of crying on the metabolism is shown in Case 22, not included in Table 3.

These tables show that muscular activity affects the basal metabolism of the premature as it does the normal infant. The maximum increase of metabolism due to activity found in this series of premature infants was about 40 per cent.

CONCLUSIONS

Determinations of the basal metabolism of premature infants are a contribution to studies of the cycle of life. The heat production is very low when calculated on the basis of total production per twenty-four hours or per unit of body surface. On the basis of the theory as to the relation of heat production to body surface, one would expect the same heat production per unit of surface as in full-term infants; but they produce less heat, and it is necessary for this reason to give the premature baby much more protection against heat loss in its period of prematurity than at any other period of infancy. The basal metabolism findings are suggestive of what the heat production of the fetus might have been during the last two months prior to birth. The basal metabolism of the premature infant is lower than that of the full-term infant, and remains so for at least three months. Even if the handicap of time is allowed, the premature infant produces less heat on his expected birthday than does the full term infant during the first week of life.

THE TREATMENT OF COLIPYURIA IN CHILDREN *

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During the thirty years that have elapsed since attention was drawn to the frequent occurrence of colipyuria in childhood, from infancy and onward, research work has been zealously pursued in an effort to find a remedy for this condition. The many methods of treatment suggested and the numerous medicaments introduced—most of them only to disappear quickly—indicate better than anything else how little success has been attained.

In cases in which there is no indication for surgical measures, such as in concrements to be removed or deformities to be corrected, an effort has generally been made to clear up the infection by urinary disinfectants given by mouth and excreted by the kidneys, or the patient is treated with alkalis administered in large doses, in an endeavor to change the reaction of the urine from acid to alkaline, and thereby eliminate the colon bacillus from the urinary duct. The vaccine treatment has been less frequently employed in pediatrics, being reserved mainly for cases in which no other treatment was effective.

Local treatment of the bladder with various antiseptics, usually silver nitrate, has been tried on a larger scale only when the symptoms indicated that the infection had localized there.

In recent years, in my own section of the hospital, I have felt more and more inclined to give preference to local treatment in all cases of colipyuria, regardless of whether they present symptoms of cystitis or of pyelitis. In this I was particularly encouraged after learning of Dr. Arne Johannesen's success with a 2 per cent. solution of silver nitrate, in the children's ward of the State Hospital (Rigshospitalet).

The method I have adopted is, briefly, as follows: Twice a week the patient's bladder is washed out with a solution of silver nitrate, 2 per cent. for the girls and, owing to the pain connected with the treatment, 1 per cent. for the boys. Hexamethylenamin methylencitrate, or phenyl salicylate was often used in addition, in doses according to age. This treatment is continued until the urine is sterile on two examinations at an interval of three or four days, i. e., it shows no growth on agar or broth after incubation for forty-eight hours.

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* Reprint of pamphlet written in honor of Prof. Thorkild Rovsing, April 26, 1922.

In the treatment of colipyuria, I attach great importance to the child's general health, improving it in every possible way. Thus other diseases that the patient may be suffering from, such as dyspepsia and anemia, are treated.

My material, drawn from cases attended in the last two or three years, includes forty-three patients, thirty-four girls and nine boys, all of whom were treated in the manner above described: forty-one at the hospital and two as outpatients.

The accompanying table classifies the patients according to age and sex. The youngest patient was 2 months old, the eldest 11 years.

In every case, the diagnosis was made by examination of the urine microscopically and by culture.

The technical side of the treatment presents no difficulties. In the case of the girls, a small silver catheter is easily introduced into the bladder, and in the case of the boys, a Mercier catheter No. 6, 8 or 10. After the urine has been drawn off, with the catheter, the bladder is washed out with from 10 to 15 c.c. of a lukewarm solution of silver nitrate, 2 per cent., in the case of the girls, 1 per cent. for the boys.

Age and Sex of Author's Patients

Age.	Girls	Boys
From 5 months to 1 year	13	8
From 1 year to 5 years	12	
5 years	9	1

In three cases, I have observed hematuria after the treatment, in which apparently the catheter had not injured the patient. The bleeding disappeared during the subsequent twenty-four hours and seemed quite insignificant. Sometimes, there is a rise of temperature after catheterization, but this is of no consequence.

Many children are quiet during the operation; others struggle and scream a great deal, and it cannot be denied that the treatment frightens them and causes them pain, particularly the boys. When children are young and cannot be pacified, we always have a bottle or something else ready for them afterward, to comfort them. For this reason, the treatment is best given in the hospital, where every convenience is at hand and everything thoroughly aseptic. Treatment should never be given in the home unless the mother is willing to cooperate.

By the method described, I succeeded in curing thirty-nine of forty-three patients. All symptoms of the disease disappeared, the urine becoming as clear as water, and free from pus and colon bacilli. The length of time required to render the urine sterile varied in the different cases, the shortest time being noted when cystitis was present, a few treatments of silver nitrate sufficing; whereas, in those cases presenting symptoms of pyelitis, a longer time was necessary. The average duration of the treatment also varied, being longer for the boys, who were all suffering from pyelitis, than for the girls, many of whom either had or, at an earlier stage of their illness, had had, bladder trouble. The treatment lasted on an average five weeks in cases in which the patient showed symptoms of having or having had cystitis; and eight weeks in other cases. As a rule, the urine soon becomes clear and the pus diminishes in amount and finally disappears. The colon bacillus persists longer; the pyuria becomes a bacteriuria, and it is this condition which ordinarily is slow to improve. Simultaneously with the clearing up of the urine, the patient's other symptoms of disease disappear; the temperature becomes normal; the appetite improves, and the weight increases. A few case histories, illustrative of the prognosis and the course of treatment, are presented herewith.

REPORT OF CASES

Case 1.—B. F., a girl, aged 8 years, who had been treated six weeks for pyuria twelve months previously at the Municipal Hospital, three days before admission to the Children's Hospital developed abdominal pains, with rise of temperature and frequent and painful urination. On admission, the urine contained pus and traces of albumin, and yielded a growth of *B. coli.* During the first eight days the temperature rose to 102.5 F.

November 26, a 2 per cent. solution of silver nitrate was employed in bladder lavage, and from November 29, 0.5 gm. of phenyl salicylate was added and the mixture employed three times a day, after which irrigation with silver nitrate was employed twice weekly.

December 7, the urine was free from pus but yielded a growth of *B. coli* on culture.

December 16-19, the urine was sterile, and treatment was discontinued.

January 4, the patient was sent home, well.

Control examination, ten months later, revealed that the urine was free from pus and *B. coli.*

Case 2.—R. N., a girl, aged 9 months, who when younger had been treated at the hospital for rachitis and trismus neonatorum, had been vomiting during the last fortnight. The bowel condition was supposedly normal and there were no symptoms of urinary disorder. The temperature on admission was 104.5 F. The urine contained pus and albumin and yielded a growth of *B. coli.*

May 27, bladder lavage with a solution of silver nitrate, 2 per cent., twice weekly, and with hexamethylenamin methylencitrate, 0.15 gm., three times daily, was prescribed.

June 18, the urine contained only a few pus cells and *B. coli.*

August 9, growths of *B coli.* were obtained.

August 18, growths of *B. coli* (a few colonies) were obtained.

August 23 and 26, the urine was clear; there was no growth, and treatment was discontinued.

There was a steady rise of temperature during the first months, but the temperature became normal during the last months. The general condition improved gradually during treatment, and, September 6, the patient was discharged as cured.

Control examination, three and a half months later, revealed that the urine was free from pus and *B. coli.*

Case 3.—K. B., a boy, aged 11 years, had complained for about a week of being tired. He had no appetite and had been vomiting. Two days before, hematuria was noted, but there was no lumbar pain, and the urination was neither frequent nor painful. On admission the temperature was 100.8 F. The urine test showed blood; albumin, 4.5 per cent. by Esbach's method; some red and white corpuscles, and casts. The first four weeks, the patient was treated for hemorrhagic nephritis. The temperature remained at 100.4 F. The urine contained less blood and only traces of albumin. Roentgen-ray examination revealed no concrements.

July 16 (four weeks after admission to the hospital), catheterization was performed and showed now that the patient had a colipyuria, for which irrigation with 1 per cent. silver nitrate was employed, twice a week.

August 8, the urine contained a few leukocytes and *B. coli*, with traces of albumin and blood.

August 13 and 16, the urine was sterile. Treatment was discontinued. The temperature was normal from August 10 on, and the patient was discharged, August 24, as cured.

Control examination, fourteen months later, revealed that the urine was free from pus and *B. coli.*

Case 4.—L. P., a boy, aged 11 months, became ill a month previously, with rise of temperature and chills. Three or four days thereafter, the physician made a diagnosis of pyuria, and treated the patient with medicine and boiled water. As there was no improvement, the child was admitted to the hospital. The temperature was 101 F. The urine contained quantities of leukocytes and *B. coli.*

November 25, orders were given for irrigation with 1 per cent. silver nitrate, twice weekly.

December 14, the urine contained a few leukocytes and *B. coli.*

December 20, hexamethylenamin methylencitrate, 0.25 gm., three times daily; was prescribed.

January 4, 7 and 12, the urine was clear and sterile. Treatment was discontinued. The temperature on a few occasions was about 100.4 F., and had been normal since December 25. The patient was discharged, January 14, as cured.

Control examination, ten months later, revealed that the patient had been well since discharge. The urine was clear, and free from pus and *B. coli.* (no growth on agar and broth after forty-eight hours).

The results in all the thirty-nine cases were, with but slight variation, similar to those of these four cases, the patient being discharged with sterile urine, apparently cured.

Besides these thirty-nine patients, I have treated four, of whom two were discharged with colipyuria and two with bacteriuria. Below is a report of these cases.

Case 5.—H. R., girl, aged 5 years, during the previous week had complained of abdominal pains, and had sometimes screamed with pain during the night. The temperature was 101 F., and there was painful urination. The temperature on admission was 100.8 F. A urine test revealed traces of albumin, numerous leukocytes and *B. coli.*

March 20, irrigation of the bladder with 2 per cent. silver nitrate, twice a week, was prescribed, and phenyl salicylate, 0.3 gm., four times daily, as well as 1 pint of boiled water daily.

April 3, roentgen-ray examination revealed no signs of calculi.

April 7, phenyl salicylate was discontinued. Hexamethylenamin methylencitrate, 0.35 gm., was employed, three times a day.

April 19, the urine contained a few leukocytes and *B. coli.*

May 4 and 11, the urine was sterile, and treatment was discontinued.

May 15, the patient was discharged as cured and sent into the country.

Three months later, she was again admitted. Four days previously, after returning from the country, she had had a rise of temperature to 102.2 F., with frequent urination. The urine contained pus and *B. coli.*

August 20, irrigation of the bladder was prescribed with 2 per cent. silver nitrate, twice a week, and phenyl salicylate, 0.5 gm., three times a day.

September 3, phenyl salicylate was discontinued.

September 4, the urine contained pus and *B. coli.*

September 5, irrigation with silver nitrate was continued, with autogenous vaccine treatment.

October 7, the urine still contained pus, though less, and *B. coli.* Treatment with silver nitrate and vaccine was discontinued. Phenyl salicylate, 0.5 gm., three times a day, was again prescribed, but this treatment seemed of benefit for only a week.

October 31, the urine still contained pus and *B. coli.* The patient was discharged, November 2.

Control examination, two years later, revealed that the urine did not contain pus, but yielded a growth of *B. coli.* The patient suffered from enuresis.

Case 6.—U. P., a girl, aged 9 years, who two years previously had suffered from nephritis, had been confied to bed during the previous week, complaining of lumbar pains. On admission to the hospital, the temperature was 100.4 F. The urine contained fetid pus, traces of albumin, and *B. coli.*

October 19, irrigation with 2 per cent. silver nitrate, twice a week, and phenyl salicylate, 0.5 gm., three times a day, was prescribed.

November 9, the urine contained numerous leukocytes, but yielded no growths of *B. coli.*

November 14, a growth of *B. coli* was obtained.

November 25, phenyl salicylate was discontinued, and hexamethylenamin methylencitrate, 0.3 gm., three times a day, was prescribed.

November 29, no growth of *B. coli* was yielded; thereafter, there was sometimes a growth of *B. coli,* sometimes none.

December 6, numerous leukocytes were noted.

December 29, the patient was discharged. The general health was good; there was an increase in weight of 5.5 kg., but the urine still contained pus and *B. coli.* The patient was not subjected to roentgen-ray examination. Control examination was refused.

Case 7.—L. J., aged 5 months, two days previously in the evening, was suddenly seized with cramp. Since then, there had been four attacks. When the patient was admitted, the temperature was 100.4 F.; in the evening, 104 F. The urine contained pus, no albumin and *B. coli.*

May 12, irrigation with 1 per cent. silver nitrate, twice a week, was prescribed and hexamethylenamin methylencitrate, 0.1 gm., three times a day.

May 20, dilation of the phimosis was done.

May 29, the urine was clear and free from pus, but yielded *B. coli.*

June 19, the urine contained no pus, but was still positive for coli.

June 25, the urine continued to yield *B. coli.* Irrigation with silver nitrate was discontinued.

June 28, treatment with hexamethylenamin methylencitrate, 0.15 gm., three times a day, was continued.

July 15, the urine contained *B. coli.*

July 18, the urine contained numerous leukocytes and *B. coli.*

July 25, hexamethylenamin methylencitrate was discontinued, and sodium bicarbonate, 0.25 gm., four times a day, was prescribed. From August 11, sodium bicarbonate, 0.25 gm., was employed, six times a day.

August 17, the urine contained pus; the bowels were loose, and sodium bicarbonate was discontinued.

September 2, the urine contained *B. coli,* but no leukocytes.

September 11, hexamethylenamin methylencitrate, 0.3 gm., three times a day, was prescribed. The patient was discharged, September 12, treatment with hexamethylenamin methylencitrate and 1 per cent. silver nitrate to be continued at home, once a month.

October 16, the urine was free from pus and *B. coli* (no growth on agar and broth after forty-eight hours). Treatment was discontinued.

Control examination, one month later, revealed that the urine was free from pus and *B. coli.*

In addition to colipyuria, the patient suffered from chronic dyspepsia during her entire stay in the hospital. This condition was cured by the time she was discharged. During the first months, there was a steady rise in temperature, but the temperature was normal during the latter months.

Case 8.—H. J., a boy, aged 5 months, who had had a rise of temperature for a week while at home, and a temperature of 101.8 F. on admission to the hospital, had pus and *B. coli* in the urine. He also suffered from chronic dyspepsia.

November 20, irrigation of the bladder with 1 per cent. silver nitrate, twice a week, was prescribed, and phenyl salicylate, 0.1 gm., three times a day.

December 7, the urine contained pus and *B. coli.*

January 1, the urine was clear but yielded a growth of *B. coli.*

January 10, the urine contained some leukocytes and *B. coli.*

February 2, the urine yielded a growth of *B. coli.*

February 21, phenyl salicylate was discontinued and hexamethylenamin methylencitrate, 0.2 gm., four times a day, prescribed.

March 18, the urine contained pus and *B. coli.*

April 4, the urine yielded pus in diminished quantities, and a growth of *B. coli.* Silver nitrate was discontinued, hexamethylenamin methylencitrate continued.

May 3, the urine was clear but yielded a growth of *B. coli.*

May 6, the patient, who was now cured of a chronic dyspepsia and whose temperature during the first months had only risen now and then, was discharged, but the treatment with hexamethylenamin methylencitrate, 0.2 gm., four times a day, and 1 per cent. of silver nitrate was to be continued at home, once a month.

November 18, the urine was free from pus and *B. coli.*

Control examination, one month later, revealed that the general condition was good. The urine was free from pus, and free from growth of *B. coli.*

COMMENT

Neither of the last two patients was examined by roentgen ray. I can give no satisfactory explanation as to why the treatment failed in these four cases. The history of these cases is similar to that of many in which the result was satisfactory. In three cases, I should, from my present experience, have continued the silver nitrate treatment considerably longer, and possibly it would have been successful. The fourth patient (Case 8) was so energetically treated with silver nitrate, during three and a half months, that prolonging treatment further could scarcely be presumed to be of any value.

If a comparison is made between my cures—thirty-nine patients cured, or at least temporarily cured, out of forty-three treated—and the results attained by others, it will be seen that their percentage of cures is not so high. At any rate, I have not seen any; not if the urine must be free from pus and sterile on two consecutive examinations, before a case of colipyuria can be pronounced cured. In this connection, I would mention some figures from Denmark[1] and from Norway.[2]

Meyer's principal treatment was as follows: "To give as much fluid as possible, boiled water and hexamethylentetramin, from 0.15 to 0.5 gm., three times a day, in some cases showing a certainty or possibility of cystitis." He employed irrigation of the bladder with a solution of 2 per cent. silver nitrate; in others, with alkaline urine, a mixture of boric acid was used, and in seven cases, *B. coli* vaccine. In a few cases, the patients were either not treated at all or were treated only with water by mouth. Meyer gives a record of sixty-eight cases, four of the patients dying from bladder conditions, while five died from other causes. Meyer believes that pyuria did not play any direct part in the cause of death. Thirty of the patients were discharged as cured, or, as Meyer cautiously adds, apparently cured, since, in the beginning, he draws his conclusions as to cure only from the fact that the urine was free from pus, without bacteriologic examination, and so does not know whether the urine in all the thirty patients was sterile when they were discharged. Nineteen were discharged with pyuria, nine with bacteriuria and one with nephritis.

Collet reports more than 100 cases, treated in various ways, fifty-three with urinary antiseptics alone, twenty with antiseptics and other treatment; fourteen with irrigation of the bladder, twelve of whom were treated with urinary antiseptics also or alkaline preparations; four with vaccine, in three of whom this was combined with other treatment, and eight alternately with alkaline preparations and other treatment.

Fifty-two of these 100 patients of Collet's were discharged as clinically cured, "with clear urine. Of these, eighteen had sterile urine, forty had pyuria or bacteriuria when discharged, and eight died."

Meyer mentions the case of a 3 year old child suffering with pyuria who was cured by silver nitrate but had a relapse, although she was discharged with sterile urine. This was also true of H. R. (Case 5), who was discharged after the urine had been examined twice, both times with negative results, but was admitted again, three months later, with a recidivation. I have noticed several times that the urine may for a long time give alternately a negative and a positive culture. Taught by these experiences, I hesitated to regard my thirty-nine patients as permanently cured. I, therefore, endeavored to secure a control examination later on. Of the thirty-nine patients, thirty were examined. One had died of bronchopneumonia, and eight did not come for examination.

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[1] Meyer, Adolf: Experiences with Pyuria in Children, 1907

[2] Collet, Arthur: Urinary Infection in Childhood, 1919.

Of the thirty patients examined, twenty-one had sterile urine. The time elapsing between discharge from the hospital and the control examination was in two cases one month, in one case, three months, and in three cases, between three and six months. In six cases, between six and twelve months had elapsed; while in the case of nine patients, more than one year had elapsed. It may, therefore, presumably be said of these patients that they are cured.

In the nine patients suffering from bacteriuria, the urine was as clear as water and free from pus but yielded a growth of *B. coli*. All of these patients were girls, six under 12 months, two between 1 year and 2 years, and one, 5 years old. Two had cystitis while in the hospital; seven, pyelitis. All patients but one who had cystitis were treated with hexamethylenamin methylencitrate in addition to silver nitrate. One of these patients had sterile urine at three different times before being discharged, the others (eight), twice. The course of the disease in these cases did not apparently differ from that of the twenty-one patients with sterile urine. Only two of these were examined by roentgen ray, and showed no calculi.

Four of the above mentioned patients were again treated with silver nitrate, two with hexamethylenamin methylencitrate in addition, and two without. All had sterile urine after one or two treatments. Three have not yet had a control examination. The fourth had a sterile urine, a month later.

Unfortunately, Meyer has not made a control examination of his thirty patients apparently cured. Collet writes that, of his eighteen patients with sterile urine, one at the control examination had bacteriuria; one has not been heard from, and sixteen had sterile urine.

By means of the control examination, it has been proved that children suffering from colipyuria cannot be said to be finally cured even if by this treatment the urine is proved sterile by two or three consecutive tests. It is necessary to follow the case after the treatment is stopped and to test the urine bacteriologically. The thirty-nine cases cured by me may, therefore, be reduced somewhat, how much it is impossible to say definitely, as the figures are so small that chance may play a part in the calculation. However, I believe that I am not far wrong in putting the percentage of patients cured at 66, when I take into account the twenty-nine patients who returned for the control examination, about two thirds of whom were finally cured.

As will be seen by the introductory remarks concerning my method of treatment, in all cases irrigation was performed twice a week, with a 1 or 2 per cent. solution of silver nitrate. In most cases hexamethylenamin methylencitrate or phenyl salicylate was employed alternately. One patient was given alkalis for a short time, and a few, *B. coli* vaccine. All the younger patients were given plenty of water and their food was principally liquids. The older ones had fruit syrup and water between meals. Their general health was given careful attention, and complications were energetically treated.

When so many methods of treatment are combined, and when, in addition, a disease follows so whimsical a course, and is not infrequently cured spontaneously, it is difficult to say definitely which is the principal factor in the result achieved. I have not the slightest doubt that it was attained by a consistent treatment with silver nitrate, or why should my results be so much better than those of others? On the other hand, it may be possible that the contemporary treatment with hexamethylenamin methylencitrate or phenyl salicylate has also contributed to the results, even if this cannot be proved.

To every one here in Denmark, where we are well acquainted with the significance of irrigation with silver nitrate as a urinary disinfectant, it is not surprising that the treatment with silver nitrate was effective when cystitis was present; but it is surprising to see a therapeutic effect attained in cases suspected to be pyelitis. I can give no reasonable explanation as regards this, unless, in far more cases than is generally believed, the infection is one of the bladder, the focus of infection being there.

I do not quite agree with the authors who consider the administration of silver nitrate to children suffering from pyuria useless, even injurious. And when the treatment has not given desirable results elsewhere, except in cases in which cystitis was present, I believe this to be entirely due to the fact that treatment was not carried out consistently and a too weak solution was administered.

THE EFFECT OF DRUGS ON BLOOD AGGLUTININS *

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Although the status of blood grouping and its value in preventing harmful reactions have been definitely established, more or less severe reactions following blood transfusions are still reported in the literature. Attempts have been made by many men to explain the phenomena observed. Unger [1] has urged the advisability of grouping the donor's blood directly against the blood of the recipient. Lately, several cases have been reported which demonstrate that our previous conceptions of hemolysis and agglutination may need some revision. Astrowe [2] has pointed out the necessity of repeated tests of donor's versus recipient's blood before each transfusion. West,[3] in a later note, cites a case in which hemolysis of the donor's cells took place without preliminary agglutination.

In January, 1922, Eden [4] advanced the theory that the agglutinins present in the blood could be changed or altered in various degrees. This change from one group to another is apparently not permanent, but persists for some appreciable time. He states that it can be obtained by the administration of various drugs; by chloroform-ether anesthesia, or by prolonged exposure to the roentgen rays (Table 1).

Later, Levine and Segall [5] reported that prolonged etherization causes a temporary change in the iso-agglutinative phenomena, thereby confirming Eden's results.

Recently, Huck and Peyton [6] reported twenty-five cases in which patients were subjected to ether anesthesia without any change in the blood groups.

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* From the Minneapolis General Hospital.

[1] Unger, L. J.: Therapeutic Aspect of Blood Transfusion, J. A. M. A. **73**:815 (Sept. 13) 1919.

[2] Astrowe, P. S.: Hemolysis Following Transfusion, J. A. M. A. **79**:1511-1514 (Oct. 28) 1922.

[3] West, P. C.: Hemolysis Following Transfusion, J. A. M. A. **79**:1950 (Dec. 2) 1922.

[4] Eden, Rudolf: Die Bedeutung der gruppenweisen Hamagglutination für die Agglutinationsgruppen durch Medikamente, Narkose, Röntgenbestrahlung, Deutsch. med. Wchnschr. **48**:85-87 (Jan. 19) 1922.

[5] Levine, E. C., and Segall, H. N.: Posttransfusion Reactions; Alterations in Blood After Ether Anesthesia and After Blood Transfusion, Surg., Gynec. & Obst. **35**:313 (Sept.) 1922.

[6] Huck, John C., and Peyton, Sarah M.: Study of Iso-Agglutinins Before and After Ether Anesthesia, J. A. M. A. **80**:670-671 (March 10) 1923.

Owing to the manifest importance of the question involved, we repeated Eden's original experiments on a series of patients. Data and results obtained are given in Table 2. The observations were made on children in our pediatric service, varying in age from 3 to 12 years. The patients were grouped before and at irregular intervals following the administration of the medication desired. The Lee method and Moss classification for blood grouping were used throughout the present study.

Table 1.—*Tabulation of Results Obtained by Eden (1922)*

Case	Original Blood Group	Drug Employed	Amount	Result	Remarks
1	III	Quinin	1 gm. for 2 days	Changed to Group I	Nine days later in Group III
2	II*	Quinin	5 gm., 1st day; 1 gm. 2d day	Group I	
3	III	Calcium lactate	0.4 gm.	Group I	
4	III	Calcium lactate	1st day, 0.2 gm.; 2d day, 0.2 gm.; 3d day, 0.2 gm.	Group I	Group III on fourth day
5	IV	Antipyrin	0.5 for 18 days	Group I	Fifteen days later in Group IV
6	IV	Solution of potassium arsenite (Fowler's solution)	2 drops 3 times a day to 8 drops 3 times a day and back; 3 drops 3 times a day (12 days)	Group II	Remained in Group II for 19 days; 23 days later, in Group III; 33 days later, in Group IV
7	IV	Chloroform-ether	....	Group III	Four days later in Group IV
8	IV	Chloroform-ether	30 min.	Group III	
9	II	Chloroform-ether	30 min.	Group IV	Three days later in Group II

* In three other patients, belonging to Group II, after exposure to the roentgen ray for long periods of time (from three to twelve hours), the grouping changed to I in one case and to IV in the two other cases.

RESULTS

It is at once apparent that our results are entirely negative. Drugs given to their therapeutic limits failed to produce any change in the iso-agglutinative phenomena. In one case (Case 11, Table 2) a patient in Group III, with a total blood volume of approximately 1,000 c.c., received 700 c.c. of Group IV blood intravenously without any change in blood group.

Von Dungern and Hirschfeld[7] believe that only two different agglutinins exist in human serum and that both are present in Group IV serum. Unger[1] has proved this in an ingenious way. Employing Group IV serum, he was able, after taking out the agglutinins for Group II cells, to obtain agglutination of Group III cells.

TABLE 2.—*Results of Application of Eden's Experiments to Authors' Series*

Case	Medication		Original Group	End-Result	Remarks
	Drug	Amount			
1	Quinin sulphate	15 grains (1 gm.)	IV	IV	
2	Quinin sulphate	15 grains (1 gm.)	III	III	
3	Quinin sulphate	15 grains (1 gm.)	IV	IV	
4	Quinin sulphate	10 grains (0.6 gm.)	IV	IV	
5	Quinin sulphate	15 grains (1 gm.)	II	II	
6	Quinin sulphate	40 grains (2.6 gm.)	IV	IV	Toxic sypmtoms
7	Calcium lactate	10 grains (0.6 gm.)	III	III	
8	Calcium lactate	10 grains (0.6 gm.)	II	II	
9	Calcium lactate	10 grains (0.6 gm.)	II	II	
10	Calcium lactate	10 grains (0.6 gm.)	IV	IV	
11	Transfusion	700 c.c.	III	III	Purpura hemorrhagica; received Group IV blood
12	Transfusion	150 c.c.	IV	IV	
13	Ether (anesthesia)*	....	III	III	
14	Ether (anesthesia)	....	III	III	
15	Ether (anesthesia)	....	II	II	
16	Ether (anesthesia)	....	II	II	
17	Ether (anesthesia)	....	II	II	
18	Ether (anesthesia)	....	IV	IV	
19	Ether (anesthesia)	....	II	II	
20	Ether (anesthesia)	....	IV	IV	
21	Ether (anesthesia)	....	II	II	
22	Ether (anesthesia)	....	II	II	
23	Ether (anesthesia)	....	II	II	
24	Ether (anesthesia)	....	II	II	
25	Solution of potassium arsenite (Fowler's solution)	1 to 10 minims, three times a day, and down	II	II	
26	Solution of potassium arsenite (Fowler's solution)	1 to 10 minims, three times a day, and down	II	II	

* Average time of administration of anesthetic was thirty minutes in each case.

The results Eden obtained would tend to show that certain drugs have the property of removing one agglutinin or both agglutinins from

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7. Von Dungern and Hirschfeld, L.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **4**:284, 1910.

the serum. It seems inconceivable, however, that an agent which apparently removes an agglutinin in one case should add an agglutinin in another case (Cases 9, 11 and 12, Table 2).

Our experiments show that the cause of reactions following blood transfusions cannot be laid apparently to any external agent. The reason may be looked for along the lines suggested by Unger and Dyke.[8]

CONCLUSION

Serum agglutinins are apparently not altered by ether anesthesia, blood transfusion or the drugs employed in the present study.

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[8] Dyke, S. C.: On Isohemagglutination, Brit. J. Exper. Path. **3**:146 (June) 1922.

A MIXED TUMOR OF THE CERVIX AND VAGINA IN AN INFANT *

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Mixed tumors of mesodermal origin, polypoid in form, often termed grapelike sarcomas, and malignant in character, are found in the vagina and also in the uterine cervix of young children. They occur more frequently in the vagina; for, while only four undoubted cases of primary mixed tumors of the cervix in young subjects have been reported, there are records of sixteen cases of primary mixed neoplasms of the vagina in children from 6 months (Hauser [1]) to 7 years (Demme [2]) of age. In addition, there are two cases in the literature in which both cervix and vagina were involved in the growth; and, although it is asserted that the cervix was the original seat of the tumor, the description of the organs at necropsy makes it impossible to substantiate this claim. The case herein reported, then, becomes the third in which the cervix was the probable seat of the primary growth, although, in view of the extensive involvement of the vagina, it was impossible to fix the point of origin.

REPORT OF CASE

History.—J. H., aged 10 months, born in the United States, of American parentage, admitted to the Babies' Hospital, April 13, 1920, was under observation sixty-nine days. The chief complaint was pallor and bloody discharge on the diaper, observed for two months. The father and mother were healthy. There had been but one pregnancy. The birth weight was recorded as 8 pounds (3,630 gm.).

The child was born at term, with normal delivery. She was nursed six months, and then a milk, water and cane sugar mixture was substituted on account of failure of the mother's milk. Some further changes made in the character of the feeding were of little importance.

Three months prior to admission, it had been noted by the mother that the stools occasionally contained mucus, and two months previously an occasional streak of blood in the stool was first noted. Some times clots of blood were observed on the napkin. The mother thought that the presence of blood on the napkins was regularly associated with the passing of urine or feces. Not infrequently, mucus and blood were noted on the same napkin. Blood was noted also on the vulva, but never in the anal folds. During this period of two months, the bloody discharge had not been constantly present, somtimes two weeks elapsing without its appearance.

The child had from four to five stools daily and urination was frequent.

Physical Examination.—The general appearance of the child was that of a well-nourished, well-developed infant, with marked pallor but not acutely ill. The admission weight was 13 pounds and 3 ounces (about 5,980 gm.). One lower incisor tooth was present. The lungs and heart were apparently normal;

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* Received for publication, May 5, 1923.

* From the Babies' Hospital of the City of New York.

the abdomen was normal in contour, and the spleen and liver were not palpable. There was no enlargement of the superficial lymph nodes.

When the labia were separated, a small amount of fresh blood was discharged, and subsequently, during a proctoscopic examination, considerable blood of very foul odor escaped from the vagina. The mucous membrane of the intestine seen through the proctoscope was normal in character, and no blood followed withdrawal of the instrument. Other physical findings were negative.

The erythrocytes numbered 2,800,000; the hemoglobin was 65 per cent.; the leukocytes numbered 14,800: polymorphonuclears, 60 per cent.; lymphocytes, 40 per cent.

The child was examined by several physicians and surgeons, and on both rectal and vaginal examination, a small, firm, bleeding mass of irregular contour, about the size of an egg, was palpated in the cervix of the uterus, extending into the vagina. The mass extended more to the left than to the right and seemed to lie close to the rectal wall, but there was no communication between the rectum and the vagina. Curettage was performed, and the material removed was examined microscopically, with the result that a diagnosis of angiosarcoma was made.

Course and Treatment.—During the period of observation in the hospital, there was progressive loss of weight, the lowest, 9 pounds and 4 ounces (about 4,200 gm.), being recorded the day the child died.

The surgeons were of the opinion that the disease had advanced beyond the stage where surgery might be of benefit. At their suggestion, radium treatment was administered (by Dr. Harold C. Bailey). The first exposure of 3 hours of 100 millicuries of filtered radium to the neck of the uterus was given fifteen days after admission. There was no bleeding from the vagina for six days thereafter, although oozing of blood had been constantly present previous to the radium treatment. After the period of 6 days it recurred, continuing at intervals until death. Three weeks from the date of admission, 1,863 millicuries of filtered radium was applied 10 cm. distance from the symphysis for three and one half hours, with a total dosage of 6,055 millicurie hours.

A slight erythema of the skin was noted after this application, and in the evening there was a rise in temperature.

One month after admission a third radium exposure of 100 millicuries was given for 300 millicurie hours. The radium was placed in the uterus with a silver wire applicator giving 0.6 mm. filter. There was no rise in temperature following this application.

Six weeks from the date of admission, the record shows that there was a fairly large conical mass felt well down in the abdomen. This mass was apparently pressing against the sacrum and coccyx. It resembled in shape an adult uterus.

The temperature was slightly elevated during the entire period of observation, with frequent rises to almost 103 F. At one time, the temperature rose above 103 F., but this was probably due to a complicating otitis. Frequent blood examinations showed a secondary anemia, varying in severity. The highest red cell count was 4,000,000, and the lowest, 1,800,000. The hemoglobin varied from 40 to 75 per cent. The highest leukocyte count recorded was 14,800; the lowest, 8,000.

A transfusion of 200 c.c. of blood by the direct method was given ten days after admission. The blood count prior to the transfusion showed 2,800,000 erythrocytes; 65 per cent. hemoglobin; 14,800 leukocytes; 60 per cent. polymorphonuclears, and 40 per cent lymphocytes.

A second blood count immediately following the transfusion showed that the erythrocytes had increased to 4,000,000 and the hemoglobin to 75 per cent.

During the child's stay in the hospital, the pallor became progressively more marked. The anorexia became aggravated, desquamation of the skin covering the abdomen occurred and trophic ulcers made their appearance on the right side of the head, two days before death, which occurred sixty-nine days after admission to the hospital.

Necropsy.—The body was that of a poorly developed and poorly nourished infant.

Lungs: There was an old fibrinopurulent pleurisy between the lobes of the right lung, with inspissated, yellowish exudate. Many subpleural, capillary hemorrhages were present over both lungs, and there was some emphysema anteriorly. The upper portion of the right lower lobe contained a small abscess, 1 by 1 cm. in diameter.

Trachea and Bronchi: These were normal. The bronchial lymph nodes were not enlarged.

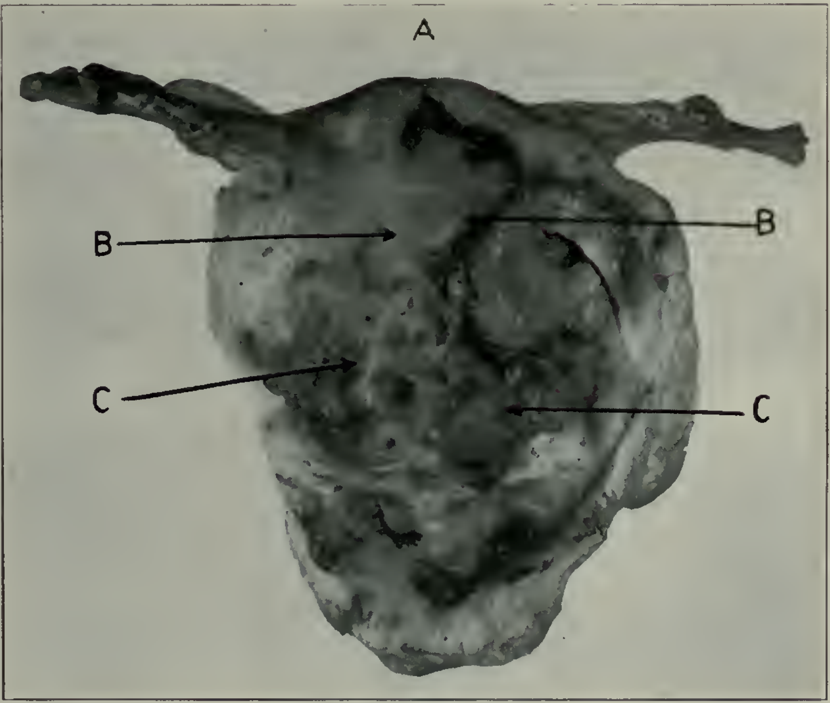

Fig. 1.—*a,* body of uterus with line of congestion on the mucosa; *b,* neck of uterus, both lips involved in the neoplasm; *c,* new growth involving the anterior wall of the vagina more than the posterior wall.

Heart: This was normal. The foramen ovale was closed.

Thymus: This was normal.

Liver: The organ was not enlarged; it was moderately fatty. Some small subcapsular hemorrhages were present on the upper surface. No metastatic nodules were present.

Spleen: Measurements were 3 by 7 cm. The organ was normal in consistency, and contained no metastatic nodules.

Stomach: There were many capillary hemorrhages in the mucosa. There were no metastases.

Pancreas: This was normal.

Kidneys: There was much swelling. The right kidney was larger than the left. The capsules were free; there was some congestion of the stars of Verheyen, and the markings in the cortex were blurred. No metastatic nodules were noted.

Small intestines: These were normal. Solitary follicles of the colon were enlarged and pigmented. In the rectum, the mucosa was deeply congested. No ulcers were present.

Pelvic peritoneum: This was deeply congested, especially over the body of the uterus. Both broad ligaments were of normal thickness and the ovaries and tubes were normal in size and appearance.

Uterus: The body measured 1.25 cm. in length and was free from tumor nodules. Its lining was congested and showed a linear area of hemorrhage extending along the entire body, just to the right of the median line. The cervix was 2.25 cm. long. The outlines of both lips and of the folds of the mucosa were lost in the tumor mass, so that only 3 mm. of the anterior lip retained its outline and free border.

Vagina: This was filled and distended with a cauliflower-like mass extending over and adherent to the entire posterior wall to a point within 0.5 cm. of the outlet. The mass also involved the lower half of the cervix uteri on the right side and the lower two-thirds on the left side. The uterine body was not involved. The greater portion of the growth was greenish black, from necrosis. A small opening through the vaginal growth into the culdesac of Douglas, just to the left of the median line, gave exit to a small amount of pus present in that pouch.

Anatomic diagnosis: (1) Neoplasm of cervix uteri and vagina; (2) purulent pelvic peritonitis, localized; (3) fibrinopurulent pleurisy; (4) pulmonary abscess, and (5) subserous hemorrhages of lungs and liver were diagnosed.

Microscopic Examination.—The first specimen submitted for examination was a collection of small pieces varying from 2 to 7 mm. in diameter, which had been curetted from the mass in the vagina. The bits of tissue were red and pink, and a small amount of clotted blood was present. On microscopic examination, four distinct points were noted: 1. There were tags of tissue from which all cell structure had disappeared, leaving the general outline of an oval, sharply limited piece taking the diffuse (eosin) but not the nuclear (hemoglobin) stain. 2. There were tags of tissue similar to those described above in size, shape and outline, but densely infiltrated with polymorphonuclear leukocytes, so that it was not possible to determine the original tissue structure. 3. There were areas consisting of blood vessels filled with red cells and having a wall of endothelial cells only. These vessels varied in size. They anastomosed in all directions, making a network of capillaries, and were surrounded by a loose stroma carrying comparatively large, irregularly round and polyhedral cells, with a clear cytoplasm and a large nucleus. Some giant cells and comparatively few spindle cells were present. There were many dividing nuclei. The picture thus presented was one of angiosarcoma, which was the first diagnosis made from these scrapings. The fourth point noted in the section was a bit composed of unstriped muscle cells, markedly infiltrated with polymorphonuclear leukocytes and partly covered with stratified pavement epithelium, the whole resembling a piece of the cervix uteri. In some fields, there were large cells resembling those seen in the third portion of the scrapings, lying around small blood vessels and between the muscle cells. The growth seemed to be of the cervical mucosa, but it had begun to infiltrate the muscle wall.

At necropsy, sections from the tumor and from the cervix and vagina beyond the growth were obtained for microscopic examination. The soft, polypoid excrescences that gave the tumor its cauliflower appearance were found to present a picture similar to that shown by the curettings, but, in addition, their relation to the vaginal wall could be traced. The large round cells were numerous and lay in a vascular stroma. Such cellular masses, with dividing nuclei, were arranged around a central stem of connective tissue, forming a finger-like process of oval or round shape. The connective tissue stem arose from, or was continuous with, the submucosa of the vagina. Some of the processes were necrotic, but some were well preserved. At the base of some processes, there were cross or long sections of younger, smaller processes composed of a vascular stroma carrying an occasional striated cell, and surrounded by the large cells characteristic of the neoplasm. The processes seemed to branch and interlace, always with masses of the large cells between them. Long cells with more or less definite striations were present, but not in large numbers, and were entirely absent in some sections. The muscle layers of the vagina showed invasion by the tumor cells, small groups of which were present between the muscle cells, lying around and sometimes within small blood vessels.

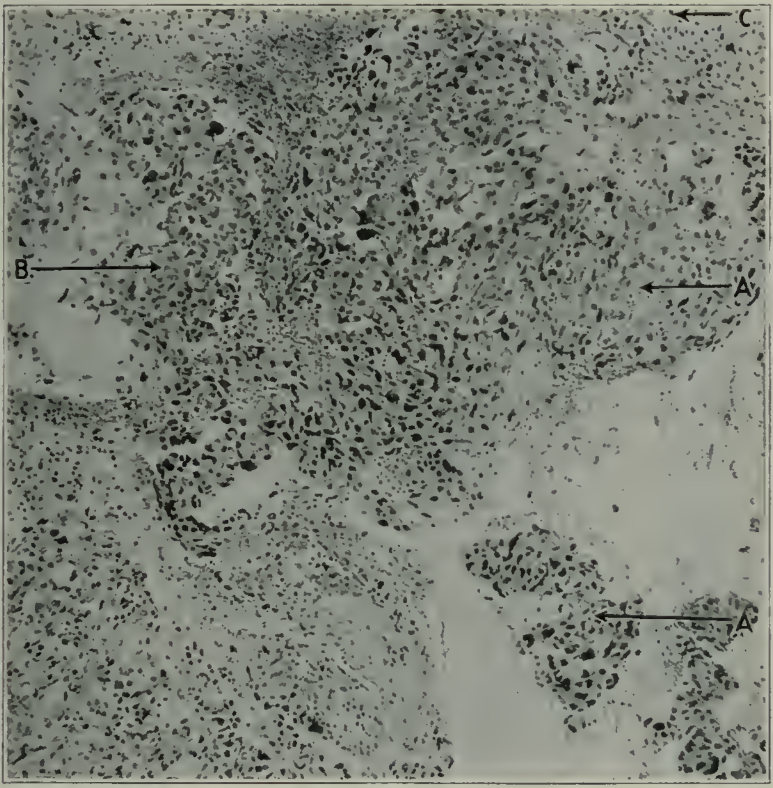

Fig. 2.—*a*, polypoid masses, with the cells, *b*, characteristic of the growth; *c*, vaginal wall. (× 130.)

The lowest portion of the vagina showed an unusual amount of striped muscle in its wall, the fibers varying much in size and shape.

In sections from the cervix, inflammatory infiltration and necrosis were very marked, and the tumor cells extended into the muscle layers.

Sections made from the vagina and the cervix beyond the neoplasm showed a loss of epithelium, and inflammatory infiltration of the mucosa and muscle wall.

From the scrapings obtained from the vagina when the infant was admitted to the Babies' Hospital, the diagnosis of angiosarcoma was made. The specimens taken at necropsy showed the growth to be a rhabdomyosarcoma, and thus brought it into the group of mixed tumors of the vagina, as classified by Wilms.[1]

COMMENT

There can be no doubt that the radium treatment altered the gross and microscopic picture by the destructive changes it introduced. No grapelike masses were seen, but both the scrapings and the cauliflower appearance of the growth at necropsy gave an indication of polypoid growth substantiated by the microscopic findings. In most cases reported, a mass has been noted as presenting at the vaginal orifice, or protruding from it. No such condition appeared in this child.

Pick [2] reported a spindle-cell sarcoma as the first primary sarcoma of the cervix to be recorded in a child. The symptoms began at the age of 2 years, and the child died six months later. There was a large uterine tumor present, extending as high as the umbilicus. It was so tightly adherent to the abdominal viscera and intestines that the latter were badly torn when an attempt was made to break up the adhesions. The tumor was grapelike in form, involving both the cervix and the uterus. The ovaries could not be differentiated.

Bluhm,[3] in 1903, reported the case of a polypoid mixed tumor of the cervix uteri occurring in a girl, 11 years old. She pointed out that Richter's [4] case (in a child, 2 years old), reported in 1892 as a proliferating mucous polyp, later examined by Grawitz and shown to be a mixed sarcoma, is really the first record of such a growth. We have been unable to obtain Richter's [4] original article. Bluhm's [3] patient recovered after hysterectomy. Wilms [1] accepts Ganghofner's [5] case, which occurred in a girl of 8 years, as a mixed tumor primary in the cervix uteri. Curtis [6] reported the case of an infant, 1 year old, in whom the growth originated in the anterior cervical lip and then involved the walls of the vagina, the anterior more than the posterior. The child died after operation. There is, in Curtis' case, no more proof of the cervical origin of the neoplasm than appears in our own.

Smith [7] reports a round-cell sarcoma of the uterus with mucous polypi, in a girl of 3 years and 9 months. Abdominal swelling and vaginal discharge were first noted eight months before operation. Numerous polypi protruded from the uterus. Smith [7] stated that several hundred of the polypi were removed through the vagina one month before the death of the patient. Wilms[1] puts this case also in the group of primary cervical sarcomas, assuming that, since the cervix was chiefly involved, the new growth originated there, as in Pick's[2] case. Nevertheless, its origin remains in doubt.

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[1] Wilms: Die Mischgeschwülste, Leipzig, 1900.
[2] Pick: Arch. f. Gynäk. **46**:191, 1894.
[3] Bluhm: Arch. f. Gynäk. **68**:236, 1903.
[4] Richter: Cited by Bluhm (Footnote 3).
[5] Ganghofner: Cited by Wilms (Footnote 1).
[6] Curtis: Med. Press and Circular, New Series **76**:51, 1903.
[7] Smith: Am. J. Obst. **16**:555, 1883.

Sarcomas of the body of the uterus are exceedingly rare in children. Rosenstein[8] has reported such a case in a child not yet 2 years old.

As for mixed tumors of the vagina, they have been reported in children from 6½ months (Hauser[9]) to 7 years (Demme[10]) of age. In Demme's case, a peasized nodule was said to have presented at the vulva at birth, but did not begin to enlarge until five years later. Operation was performed at the age of 5½ years, when the growth had become as large as a peach. There were two recurrences, and the child died at the age of 7 years. Schuchardt[11] reported two cases. One of these children, 2 years old, showed a recurrence of the tumor six and one half months after operation. A second operation was performed, and the child made a complete recovery. Ten years later, she was in "blooming health," as Schuchardt wrote to Holländer[12] when the latter reported the case of a 9 months old baby who recovered after an operation for removal of a vaginal polypoid sarcoma.

The tissue elements which have been described in these mixed neoplasms of the vagina and cervix are: round and spindle cells, in practically every case reported; myxomatous tissue, wherever a polyp has been examined; unstriped muscle, rarely; striped muscle, more rarely still, and cartilage. All these elements are of mesodermal origin.

Though these tumors are malignant, they rarely metastasize to distant organs by way of the blood or lymph stream. They do extend locally, involving the bladder, parametrium and broad ligaments, and, rarely, the regional lymph nodes (Curtis[6]). They are congenital tumors, originating from cells of the mesoderm, whose embryonal potentialities are expressed in the mixed elements present in the growth. The undifferentiated cells are transported to the seat of their later development (uterus or vagina) by the Wolffian duct as it grows caudalward.

The prognosis of mixed sarcomas of the vagina and cervix in young children is bad, but not hopeless. Radical operation has resulted in cure in three cases: an 11 year old girl with a polypoid mixed sarcoma

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8. Rosenstein: Virchows Arch. f. path. Anat. **92**:191, 1883.

9. Hauser: Virchows Arch. f. path. Anat. **88**:165, 1882.

10. Demme: Cited by Pick (Footnote 2).

11. Schuchardt: Deutsch. Gesellsch. f. Gynäk., Second Congress, 1888, p. 237.

12. Holländer: Deutsch. med. Wchnschr., 1896, 22d Society Proceedings, No. 16, p. 102.

of the cervix uteri (Bluhm[8]); a 2 year old child with polypoid mixed sarcoma of the vagina (Schuchardt[11]), and an infant, 9 months old, with a polypoid mixed sarcoma of the vagina (Holländer[12]). In not one of these cases in which cure was reported were any striated muscle elements found in the tumor. Their presence is, apparently, accompanied by a greater degree of malignancy.

INDURATED ULCER OF THE TONGUE DUE TO OIDIUM LACTIS *

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Oidiomycosis of the tongue, characterized by an ulcerating granuloma, is apparently a rare affection. We have not been able to find any description of cases similar to the one recently studied here, in which both the pathologic lesion of the tongue and the micro-organism concerned in its development presented unusual features.

REPORT OF CASE

History.—H. L., a male infant, had been under feeding care at the Harriet Lane Dispensary from the age of 4 months. The family history was negative. The mother had been compelled to wean the baby when he was 2 weeks old, and he had never gained weight. July 15, 1922, when first seen, he weighed 8 pounds and 14 ounces (4,025.6 gm.). His feedings were adjusted and he gained slowly until September 12, when he weighed 9 pounds and 12 ounces (4,422.5 gm.).

September 17, he became suddenly ill, with vomiting, diarrhea and fever. He passed five or six watery, greenish stools daily. September 25, the mother noticed a considerable amount of mucus and a fleck of blood in one stool. At this time, a sister, 2 years old, was suffering from a typical attack of bacillary dysentery, with characteristic bloody, mucous stools. On the basis of this, our patient's diarrhea was diagnosed dysentery, although no further blood was seen. We were unable to obtain a satisfactory mucous stool for culture. At this time, the mother first noticed a "sore" on the child's tongue.

Physical Examination.—The patient was a small, puny and emaciated infant. He was now 6 months old, and weighed 8 pounds and 15 ounces (4,054 gm.). He was pale and sallow; the skin was loose; the tissues were flabby, and there was no subcutaneous fat. The child was irritable and hypertonic, but not drowsy or dehydrated. The examination was otherwise negative except for the tongue. An ulcer was situated in the midline far back on the dorsum, about 2 cm. in front of the epiglottis. It was circular in shape, about 8 or 10 mm. in diameter, and 2 or 3 mm. deep. The edges were slightly raised and slightly undermined. The surface and overhanging edges were covered with a dirty grayish fur. The margins and base of the ulcer were hard, almost like cartilage in consistency, and felt like a button. The rest of the tongue and the mouth were entirely normal in appearance. No other ulcerations were seen, and there were no whitish flecks suggestive of thrush. The submental and the cervical lymph nodes could not be felt.

The indurated character of the ulcer was so striking that it immediately suggested a granulomatous process of some nature. The baby was tested with 0.1 mg. of old tuberculin, intradermally, and gave no reaction. A Wassermann test of the blood was negative, and a roentgenographic examination of the bones revealed no evidences of syphilis. Three weeks later, October 19, the

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* Received for publication, May 17, 1923.

* From the Department of Pediatrics and the Department of Pathology and Bacteriology, Johns Hopkins University.

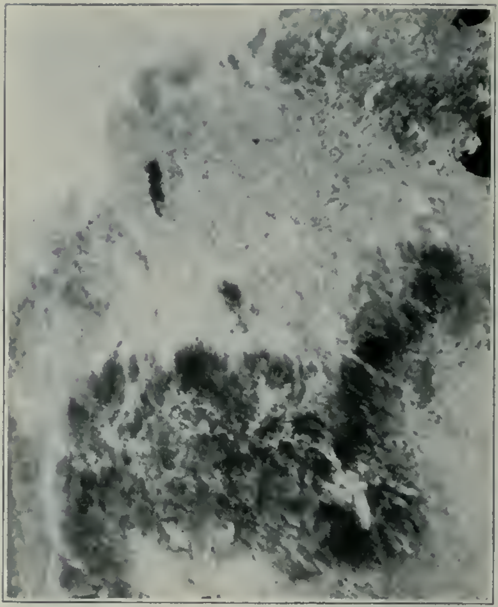

Fig. 1.—Section of edge of ulcer of the tongue. The dark-staining masses are composed of the growth of Oidium in the necrotic tissue of the tongue. (Hematoxylin and eosin stain; × 100.)

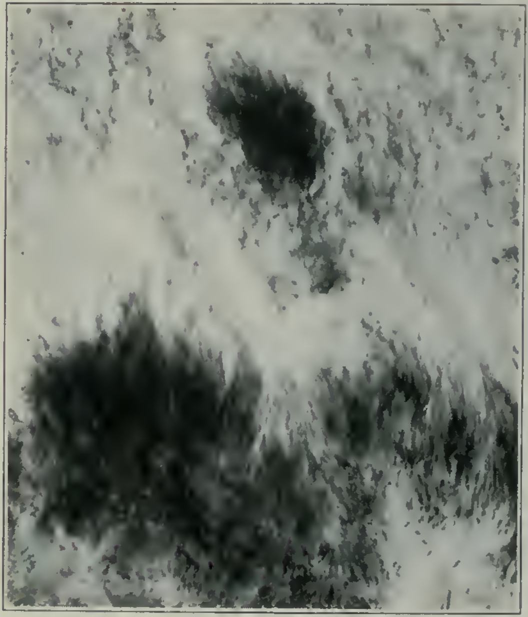

Fig. 2.—Section shown in Figure 1 (× 500). The mycelial filaments of Oidium in the tissue around the ulcer of the tongue can be seen.

ulcer had not improved, and presented the same characters as before. Scrapings from the ulcer were examined under the dark field and stained with Noguchi's stain for spirochetes. No spirochetes were seen, but many yeastlike bodies and some mycelial threads were noticed. October 23, a small piece of tissue was removed from the edge of the ulcer with a curet. Sections were made and stained with hematoxylin and eosin. Cultures were also made on Sabouraud's maltose agar.

Microscopic Examination of Section.—The section from the tongue did not contain any recognizable epithelium. The tissue was composed chiefly of granular and coarsely fibrillated material which was stained diffusely with eosin and was stippled with bluish black dots of degenerated nuclei. The outer surface of the tissue was marked with a blue staining rim, and masses of this blue staining material projected downward into the red necrotic substance of the tongue (Figs. 1 and 2). The blue staining masses were composed of curved and parallel rows of granular threadlike structures with a definite contour. Septums and branches were recognizable among these mycelial filaments, especially at the thinner edges. Linear extensions of the mycelial processes penetrated the deeper portions of the tissue. There was no significant infiltration with leukocytes. No other micro-organisms, no forms of actinomyces and no budding forms were found in the section. The threadlike structures were undoubtedly the mycelia of a fungus.

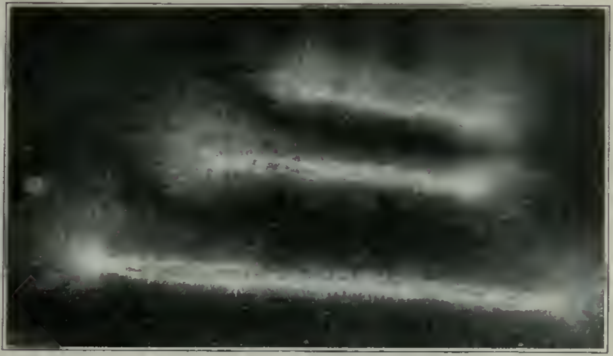

Fig. 3.—Growth of the Oidium on the surface of Sabouraud's maltose agar (natural size), showing whiteness of the growth, and filamentous edges formed by mycelia extending over the agar.

Description of the Fungus.—The material scraped from the ulcer of the tongue was planted on Sabouraud's maltose agar, p_H 6. The organism to be described below grew readily in this medium, both at 18 C. and at 37 C. The colonies were at first flat and semitranslucent, with delicate filamentous edges. After four days, the colonies were elevated and more opaque in the center. and the edges extended in a hazy fringe of interlacing filaments. The growth was at first whitish gray, and later slightly yellowish. A stroke culture on Sabouraud's agar at the end of a week resembled a centipede (Fig. 3). The filamentous edges of the culture were at first of long straight mycelia, with few septums and with forked dichotomous branching at their ends (Fig. 4). These structures exactly correspond with the form of growth of the organism seen in the section of tissue from the tongue (Fig. 2). Later, these mycelial filaments segmented abundantly, forming rectangular cells, with rounded corners.

The morphologic changes of the organism during its growth were followed by the continuous observation of cultures in hanging drops. A round cell, or

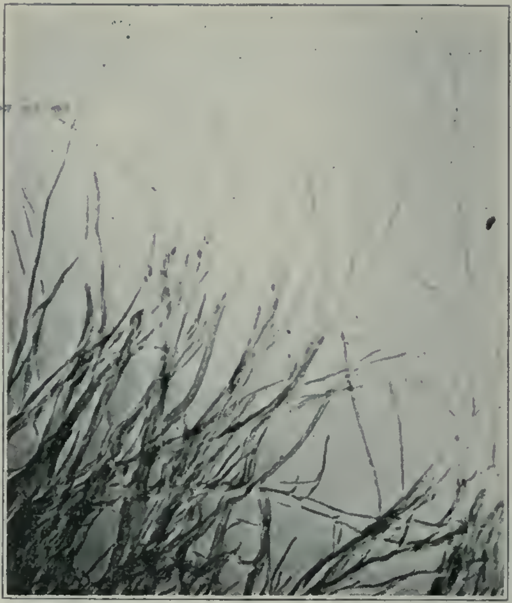

Fig. 4.—Mycelial filaments composing the edge of a growing colony. Dichotomous branching shown at ends of mycelia. These filaments were similar to those seen in the section from the tongue; × 500.

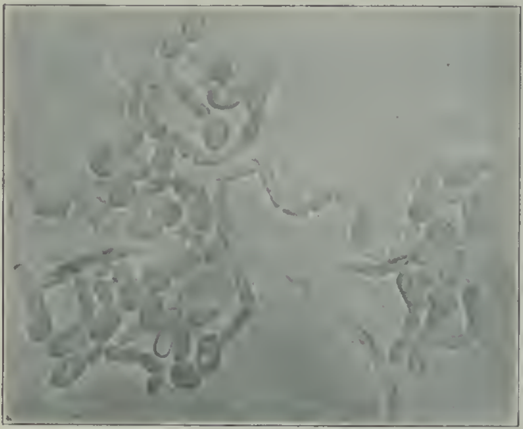

Fig. 5.—Unstained cells of Oidium in culture in a hanging drop. Large rounded forms, budding forms, rectangular cells with rounded edges and a mycelium are shown; × 1,000.

one of the elongated rectangular cells with rounded corners, extruded a bud at one corner of the cell. Some cells produced two buds. From the bud, two types of structures developed. In some cases a rapid regular sequential segmentation of the growing cells occurred, producing a chain of rounded, though almost rectangular, cells. In others, the bud grew out as a long hyaline tube, with double contour. This extended to a considerable length before segmentation occurred. Many of the mycelia branched at the extremities, forming a Y-shaped fork. Nuclear structures, vacuoles and various large and small granules were seen in the cells (Fig. 5).

The organism grew readily on ordinary culture mediums and in solutions of various carbohydrates in 1 per cent. peptone water, at p_H 7.4. A thick furry pellicle was formed on the surface of the liquid medium. The cultural reactions may be thus summarized: dextrose: acid produced without gas; lactose, sucrose, mannite and xylose: unchanged; milk: slightly acid, without coagulation; gelatin: not liquefied; Loeffler's serum: not liquefied. An identical organism was isolated from the feces.

As these morphologic and cultural characteristics are identical with those of *Oidium lactis*, this organism was compared with a type strain of *Oidium lactis* obtained from the Department of Agriculture at Washington. No difference between the two strains could be detected. On the basis of these data, the organism isolated from this patient was classified as *Oidium lactis* Link 1809. It is included in the genus *Oidium*, as emended by Pinoy to contain human parasites.

Oidium isolated from this ulcer of the tongue was not pathogenic for guinea-pigs and rabbits.

Agglutination.—The serum of the patient agglutinated a suspension of the culture of *Oidium* isolated from the ulcer of his tongue. Agglutination was definite in a dilution of 1 to 80 of the serum. The serum from several normal individuals did not agglutinate this organism.

Subsequent Course and Treatment.—Because of the loose stools, protein milk was prescribed. The diarrhea gradually responded to this treatment, and the baby began to gain in weight. December 28, the feedings were gradually changed to whole milk mixtures. Jan. 29, 1923, the child was doing well, and weighed 15 pounds and 3 ounces (6,888 gm.).

After the fungus had been identified, treatment of the ulcer was begun. October 27 to November 13, it was painted with tincture of iodin every third or fourth day. It became slightly smaller, but did not appear to be healing satisfactorily. November 13, cultures from the ulcer were again made, and the fungus was found to be present still in abundance. On the same date, the stool, which was of the claylike consistency seen with protein milk feedings, was also cultured on Sabouraud's medium. The fungus grew in great profusion on the slants. November 13, the ulcer was cauterized with a silver nitrate stick. When seen several days later, it was greatly improved. Three subsequent cauterizations, at intervals of one week, sufficed to heal it completely, leaving only a small scar.

Five weeks after the ulcer had healed completely, cultures were taken from the tongue and from the feces. No fungi grew in these.

COMMENT

A number of lesions of the mouth have been attributed to the pathogenic action of various species of *Oidium*. The most common of these affections is thrush, which has been shown to be caused by species of *Monilia* as well as varieties of *Oidium*. In thrush, there are usually multiple white flecks scattered over the mucous membranes of the mouth. The ulcerations are superficial, and the condition is often readily cured. Castellani[1] and others have described infections of the tonsils and fauces, caused by varieties of *Monilia* and *Oidium*. In these infections, there is usually a thick dirty membrane, grayish or yellowish white, over the tonsil. Both tonsils are likely to be involved, and the membrane resembles that seen in diphtheria. We have been unable to find any report of a chronic indurated ulcer of the tongue due to *Oidium*.

There is sufficient evidence in this case to assume that the fungus isolated was the cause of the ulcer of the tongue and not merely a casual inhabitant of the mouth, or a saprophyte growing in necrotic tissue. The ulcer was chronic and indurated, and of a character not usually encountered in lesions in an infant's mouth. The microscopic section showed dense masses of mycelial threads penetrating deeply into the necrotic tissues of the tongue. No bacterial invasion was seen in the section. The fungus was agglutinated by the patient's serum and was not agglutinated by normal serum. The fungus was not found in the baby's mouth after the ulcer had healed.

The presence of the fungus in the stools is probably not of significance beyond indicating that it can be swallowed and passed through the intestinal tract without losing its viability. The association of diarrhea recalls the etiology which has been claimed for *Monilia* in sprue, but in our case there is not sufficient evidence to link the diarrhea with the presence of the *Oidium* in the stools. In all probability, the child was suffering from bacillary dysentery.

SUMMARY

In a chronic indurated ulcer occurring on an infant's tongue, the mycelial filaments of a fungus were found in great profusion in the ulcer, penetrating deep into the tissues. This fungus was isolated and identified as *Oidium lactis*. It was strongly agglutinated by the patient's serum.

The ulcer did not show much improvement after local applications of tincture of iodin, but yielded readily to cauterization with silver nitrate.

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[1] Castellani, Aldo, and Chalmers, A. J.: Manual of Tropical Medicine, Ed. 3, New York, Williams Wood & Company, 1919, pp. 1093 and 1739.

SOME ASPECTS OF NEUROPATHY IN INFANCY *

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Neuropathy, by some neurologists, is said to be an acquired rather than a congenital disease. This opinion may be explained by the sphere of action of these specialists, which only very seldom permits them to study these cases in children. Otherwise, the fearful shrieks of these little ones, piercing through the closed door of the waiting room, and enabling the physician, even at a distance, to make a diagnosis with almost unfailing certainty, would long since have altered their views on this subject. A visit to the infant's ward of our hospital might serve the same purpose. We could show them the child suffering from pylorospasm and the ruminating child, the infant whose fits of restlessness and shrieking cannot be explained by bodily ailments, the baby who, after violent opposition to any variation in its diet, almost collapses from exhaustion and its fellow patient who obstinately refuses to take its feeding bottle from the hands of a strange nurse, as well the little one whose pleasure at being a center of interest makes it insensible to the pain of electric examination. Besides, we could present some patients that lie with the head bent more or less backward, without showing any symptoms of an inflammation of the ear or of an organic cerebral disease. All these peculiarities appear in infants only a few weeks, or months, old.

In these pages some observations will be made concerning three infants that presented a strong backward curve of the head.

In the second edition of Finkelstein's well known "Lehrbuch der Säuglingskrankheiten," we find an illustration of a neuropathic infant (page 191) that, besides holding its mouth open and having the small hair tuft (Freund's *Haarzopf*), is remarkable for the backward bend of the neck.

CASE 1.—Infant A, admitted to the Emma Hospital in 1915, lay in a queer attitude, which, according to the mother, it had adopted shortly after birth. The head was thrown back in such a way that the position of the face had become horizontal. The arms were folded and the legs were bent and drawn up to the abdomen. There was no question of contraction, nor did the attempts to alter the position of the infant, meet with any resistance; on the contrary, the muscles were very flaccid. As soon as the child was left to itself, it resumed its former position. It was in a state of pedatrophy. The weight, at the age of 7 months, was only 3,210 gm. The child was very pale and

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* Received for publication, March 8, 1923.

restless. It ruminated, turned and shook its head, vomited frequently and continually moved its tongue forward and backward. The peristaltic waves of the stomach were slightly visible. The heart and lungs were normal, as was also the urine. There was a slight degree of tympanites of the abdomen. At times the backs of the hands and feet were somewhat edematous. The fundus oculi was normal, and the Wassermann test was negative. Besides the characteristic attitude of the patient, the most striking feature of the case was the intermittent or periodic respiration, which continued almost without interruption when the child was asleep as well as when it was awake. Figures 1 and 2 (taken by Dr. J. B. Polak) sometimes resemble the Cheyne-Stokes type of respiration and sometimes that of Biot. There never was any sign of dyspnea. The child died at the age of 10½ months.

The mother, as well as her family, had a very nervous disposition. A sister of the patient, born later, suffered from pavor nocturnus and somnambulism. To our great suprize, after obduction had been performed by Dr. Schippers, our diagnosis of "a liquid in the brain probably in the medulla oblongata, near the respiration center" proved to be wrong. The central nervous system and the nervi vagi were very carefully examined by Dr. Brouwer of the Central Institute for Brain Research, who did not find any abnormalities. In fact, these preparations now serve in the institute as a comparative series of a normal infant. The result of the rest of the postmortem was also negative, except that it showed a slight fatty degeneration of the liver. We could not even find a focus of pneumonia. Thus, the child evidently died of pedatrophy.

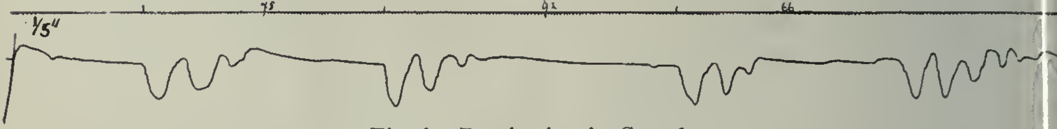

Fig. 1.—Respiration in Case 1.

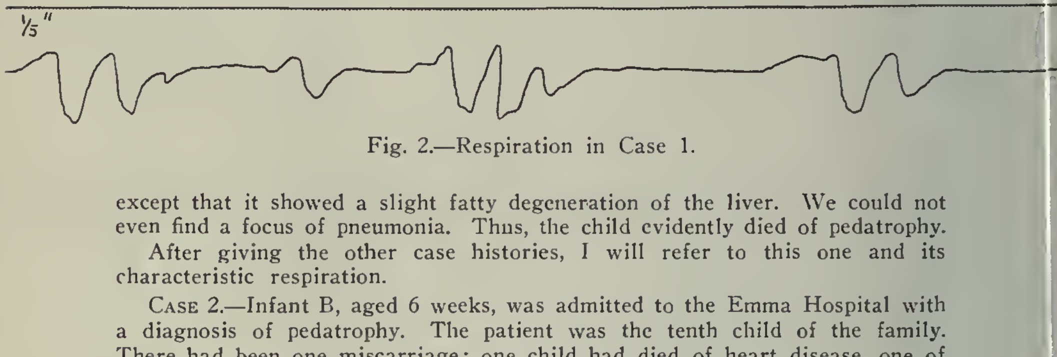

Fig. 2.—Respiration in Case 1.

After giving the other case histories, I will refer to this one and its characteristic respiration.

Case 2.—Infant B, aged 6 weeks, was admitted to the Emma Hospital with a diagnosis of pedatrophy. The patient was the tenth child of the family. There had been one miscarriage; one child had died of heart disease, one of enteritis and one of a cerebral illness. The other children, as well as the father, were in good health. The mother was queer and very nervous. She stammered. The family were Mormons, of whom there are a small number in Amsterdam. The child's birth had been normal and at term. It had been bottle fed. During the previous three weeks, it lay with its head bent far backward. It was very thin and pale and weighed only 2,930 gm. The fontanel was somewhat sunken. The face and skull were slightly asymmetric. The back presented a lordotic curvature; the arms were folded, and the legs bent upward toward the abdomen (Fig. 3). Though it was possible to change this attitude without any resistance being offered, the child resumed it as soon as it was permitted to do so. The head was always bent backward, even during sleep, and it fell back as far as possible when the child was placed in a sitting position. (In normal babies of the same age it falls forward.) The knee jerks were pronounced; the plantar reflexes were feeble and the Achilles reflex was absent.

The child had an angiospastic pallor, as is shown by the blood examination: hemoglobin (Sahli) 95 per cent.; erythrocytes 5,230,000; leukocytes 19,400; differential count: polymorphonuclear neutrophils, 33.3 per cent.; eosinophils, 0.6 per cent.; lymphocytes, 63.6 per cent.; transitionals, 1.3 per cent.; Türck's forms, 0.6 per cent. The urine was normal. The result of the electric examination of the nervus medianus was: cathodal closing, 4; anodal closing greater than 5; anodal opening greater than 5; cathodal opening greater than 5. The respiration was irregular. The patient gave a reaction to Klose's[1] suspension tests such as might be expected in a hypotonic infant. The child was hoarse and restless. It screamed a great deal, generally lay with the mouth open and ruminated. There was the little tuft described by Freund. The child did not often vomit. Still the stomach sometimes clearly presented the shape of an hour-glass. The temperature was low.

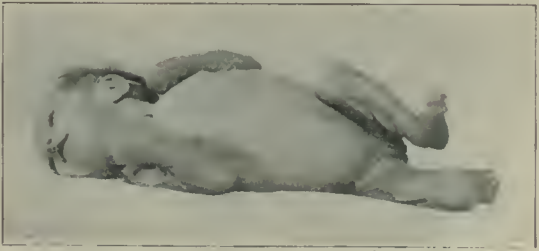

Fig. 3 (Case 2).—Appearance of child on admission.

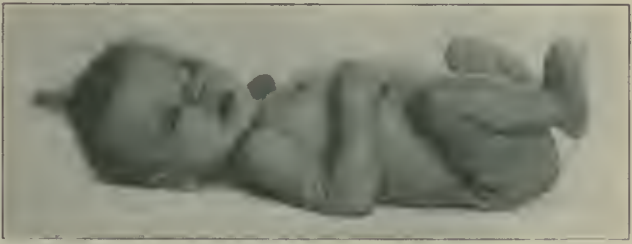

Fig. 4 (Case 2).—Appearance of child after marked improvement.

At first but little change was noted. After a while, however, the restlessness abated. The child was often found lying in a normal position, though at intervals it resumed the former attitude, with the strongly curved back and head. The dyspepsia diminished, especially so after breast milk became available. During a stay of two months in the hospital, the increase of weight amounted to nearly 1 kg. The child laughed at times and began to look around, giving an impression totally different from that given previously (Fig. 4). The suspension tests now more or less approached the type of a hypertonic infant. It was no longer possible to make the child stroke its face with the sole of its foot. During the following months, the child developed remarkably well and appeared no different from a normal baby of the same age. Only now and then it resumed the old position.

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[1] Klose: Jahrb. f. Kinderh. **82**:347, 1915.

Case 3.—Infant C, aged 3 months, was admitted to the Emma Hospital with high fever, which had lasted for some days. He was breast fed for four weeks. Afterward he was given diluted cow's milk with a small quantity of flour. Examination revealed that the left shoulder was swollen. There was an abscess on the right thigh and a small one on the back. Besides, the child suffered from otitis media. It stiffened its neck and kept it bent slightly backward. The condition improved following judicious treatment, but the child had then contracted the habit of a flaccid opisthotonus (contradictio in terminis). Even during sleep it showed a preference for a position in which the head was bent backward. No difficulty was encountered in making it bend the head forward. The muscles offered no resistance, but, like the patient mentioned above, it evidently preferred the other position (Fig. 5). At times it lay in the natural attitude. The pallor of this infant also was remarkable (angiospastic pallor; hemoglobin, 87 per cent.). It vomited habitually. The mother was very nervous. The merest trifle made her cry, just as it did her mother, whose husband, the child's grandfather, was given to drink.

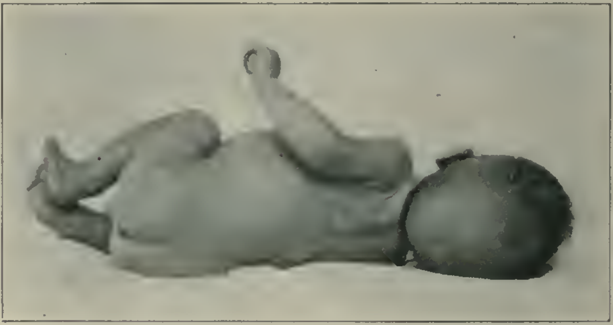

Fig. 5 (Case 3).—Appearance of infant.

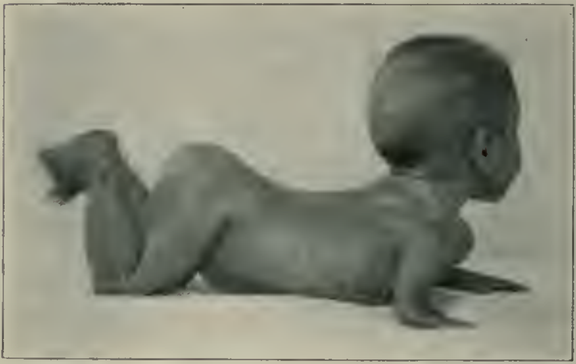

Fig. 6 (Case 3).—Appearance of infant, showing preferred position.

The baby's knee jerks were rather strong, whereas the Achilles reflexes failed. In response to the suspension test, the child behaved as does a hypotonic infant. The muscles, especially the gastrocnemii, did not feel hard. The result of the electric irritations of the nervous medianus was: cathodal closing, 3.5; anodal closing, 3.5; anodal opening, greater than 5 and cathodal opening, greater than 5. The respiration was regular. When the abscesses were cured, the dyspepsia diminished, and the child became more lively. It assumed another attitude, although it still adhered to the backward position of the head. It lay on the abdomen with the head bent far backward and slightly turned to the left, lifting the knees from the mattress and bending the legs in such a way that the heels almost rested on the strongly raised buttocks. Generally, it kept its balance by lying on the abdomen and one forearm, but sometimes it lay on the abdomen and one knee (Fig. 6), remaining in this position for a long time, evidently preferring it. By comparing Figure 6 and and Figure 7, which represents a normal child lying on the abdomen, one is impressed by the great difference. After a while the child gave up this queer position and generally lay on his back normally. Afterward, when the dyspepsia was quite cured, the infant exhibited symptoms of exudative diathesis, eczema, strophulus and asthmatic bronchitis. At the age of 10 months, the child was dismissed from the hospital. Its mental condition was quite normal.

A few weeks afterward it was again admitted, the eczema having become worse. It no longer bent its neck backward, balancing on the abdomen, but now it delighted in throwing the head from right to left and from left to right when going to sleep and when awaking (the stereotypy, called jactatio capitis nocturna by Swoboda).

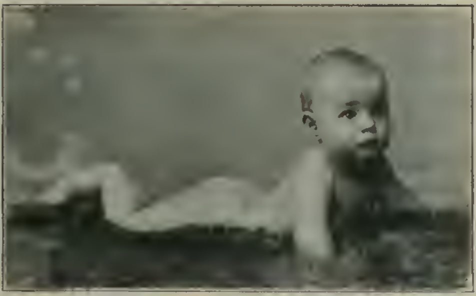

Fig. 7.—Normal child.

COMMENT

In the foregoing cases, we evidently have to do with neuropathic infants that are subject to compulsory attitudes ("Zwangslagen"). In Case 3, the attitude developed after an otitis media and an inflammation of the shoulder. In practice, we can often trace the nervous tics of older children to some slight previous ailment; for example, nervous cough may be traced to a pharyngitis; a facial tic to a corpus alienum in the eye. These three patients were not hypertonic; consequently I do not refer to Hochsinger's [2] myotonia, nor to cases of hypertonia in infants as described by Heim [3] and Klose,[1] in which opisthotonus may appear, although it very rarely does. Nevertheless, it is interesting to note that my second and third patients in their reconvalescent period were no longer hypotonic, but rather verged on hypertonia. This leads me to conclude with Heim that hypertonia is caused by neuropathy, whereas Klose believes that metabolic disturbances come first and bring forth the hypertonia by means of reflex. In the cases reported herewith, an excessive use of carbohydrates in the food was absent. Next to the backward position of the head, the most striking feature was the bent legs. That the arms were likewise bent is of less consequence, since the majority of young infants adopt this attitude. These neuropathic symptoms disappear along with the signs of dyspepsia, since hypersensitive infants are more easily influenced by digestive troubles and in quite a different way than are normal babies.

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[2] Hochsinger, C.: Myotonie der Neugeborenen und jungen Säuglinge, Monographie, 1900.

[3] Heim, P.: Berl. klin. Wchnschr. **25**:1167, 1914.

These infants will probably, in their future life, be afflicted by enuresis nocturna, somnambulism, pavor nocturnus, tics, nervous anorexia and phobias; in short, by any of the manifold expressions of a disturbed nervous system.

The periodical or intermittent respiration, as Hazelhoff[4] only recently remarked, cannot be satisfactorily explained by means of chemicophysiologic research and thought alone, but it requires the help of psychology. The psychic complex of respiration lies directly under the threshold of our consciousness, and, as we know, is much influenced by it. Thus, patients that exhibit the Cheyne-Stokes symptom always are in a state of strongly abated consciousness.

Secondly, it has been proved by Herzog's[5] investigations that Breuer's theory of the "Selbststeuerung der Atmung" must be applied to man as well as to animals. As Breuer learned from his experiments, every inspiration is checked and consequently shortened by stimuli, which spread through the lung vagi. Besides, the respiratory movements stop automatically on reaching a certain width, and, finally, an inspiration is caused by the diminishing of the lung volume. In man, the normal rhythm of respiration is not only regulated by the functions of the respiration center, but also by its self-government, which depend on the lung vagi and on the brain cortex. Though there is more time needed for an expiration than for an inspiration, the proportion never is 2 to 1, but generally is 1.8 to 1. Deviations from normal, accompanied by a normal gas metabolism and a normal circulation, imply an impaired autonomy. As Herzog also demonstrated from nine cases, Cheyne-Stokes respiration, besides exhibiting its well known characteristics, is peculiar because of an altered quotient E/I. At the beginning of each period, the inspiration was abnormally long, the exspiration being proportionally short; whereas, in the end, these conditions were reversed. In four of his cases, the inspiration, at the beginning of each period, actually lasted longer than the expiration. In cases of cardiac failure, on the contrary, the autonomy remains unimpaired. A careful examination of the expiration curves of my patient in Case 1 (Figs. 1 and 2) shows the repeated occurrence of the inspiration, indicated by the downward curve, being absolutely longer than the expiration, indicated by the upward curve. This led me to consult the literature on respiration curves of the Cheyne-Stokes type and other types, expressing rhythmic deviations of a physiologic nature, such as may be observed during sleep and in those nervous disorders which until now have been called functional. By this study, I tried to ascertain whether the altered quotient I/E was also to be found in other curves. This proved to be the case; for example, in Mosso's [6] curve of a sleeping man, aged 77 years, in whom the Cheyne-Stokes symptom disappeared as soon as the patient began to awake; as well as in a curve of an hysterical girl, Lea, aged 18, whose case was reported by Raymond and Janet.[7] Then there are curves of irregular breathing in nervous diseases; i. e., of rhythmic deviations, which, though differing from the Cheyne-Stokes type, still repeatedly present the symptom of the inspiration being absolutely longer than the expiration. (Compare Figures 8 and 10 in Beyerman's [8] essay on "Hysteria and Respiration.") Besides, Kellog [9] relates that, in cases of insanity, he found alterations of rhythm, whereas hysterical mania repeatedly shows a lengthening of the inspiration period.

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[4] Hazelhoff, F. F.: Nederlandsch. Tijdschr. v. Geneesk. **2**:910 (Aug. 26) 1922.

[5] Herzog, F.: Deutsch. Arch. f. klin. Med. **124,** 1918; ibid. **138,** 1921.

Considering that in the foregoing cases the autonomy of respiration was impaired, that the patient Lea by concentration of thought and by this only, could restore the natural rhythm,[10] and that intermittent or periodic respiration during sleep must be explained physiologically; and reflecting on Hazelhoff's remark concerning the deep sinking of consciousness which accompanies Cheyne-Stokes respiration, we are evidently justified in attributing the case of our little patient to a functional derangement of the brain cortex, the more so, since the gas metabolism and the circulation were normal and there was no trace of any organic brain disease. Here also I perceive a deep sinking of consciousness, caused by neuropathy (similar to the hysteria of Raymond and Janet), and I believe that the intermittent respiration may be explained by a periodic increase or diminution of the autonomy, as far as it is regulated by the brain cortex. Moreover, I must emphasize that infants, when

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6. Mosso: Arch. ital. de Biol. **7,** 1885.

7. Raymond and Janet sent a copy of their treatise to Dr. Beyerman, who lent it to me. The periodical in which it was published was not mentioned.

8. Beyerman: Geneesk. Bl. u. Klin. en Lab. v. d. Prakt. Series 8, No. 7.

9. Kellog: J. Nerv. & Ment. Dis., March, 1893.

10. "Thus by a totally different process Raymond and Janet came to the same conclusion which I found by experimens (namely cortical localization)" says Beyerman (Footnote 8, page 13).

awake as well as when asleep, often breathe irregularly. It looks as if the system at this age cannot function quite faultlessly. In neuropathic infants, this irregularity seems to be more pronounced than in normal ones. Hysterical hiccup repeatedly presents a ternary and a quaternary type, in which the series of shocks alternate with pauses of about equal length.[11] From Knapp's [12] investigations, we are led to seek the diaphragm center in the base of the second frontal convolution, whereas perhaps a second center may be found in the base of the precentral convolution. The field of functional nervous diseases is becoming narrowed. Perhaps the day will come when, in these cases also, an anatomic basis may be found.

The complex discussed in these pages is of rare occurrence. Besides the cases reported here, I have met it thrice in outdoor patients, who by totally overcoming the abnormal position of the head, may be said to belong to the type which I described. Therefore, we should be very careful in making this diagnosis, and should do so only in exceptional cases after long clinical observation in which special attention has been paid to the fact that there is no rigor, no opisthotonus, but that, on the contrary, the muscles are flaccid. As a rule, an infant that lies with its head bent backward is suffering from some organic disease. In such a case we should make a sad mistake if we should set the parents at ease about the state of their child.

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[11] Gilles de la Tourette: Traité clinique et thérapeutique de l'hystérie **2**:182, 1895.

[12] Knapp: Monatsch. f. Psychiat. u. Neurol. **50**:333, 1921; cited from Arch. f. Klin. d. heilk. **71**:316, 1922.

GASTRO-ENTEROSPASM AS A MANIFESTATION OF AUTONOMIC IMBALANCE IN EARLY INFANCY*

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ST. LOUIS

This paper has for its object the clearing up of certain etiologic and therapeutic misconceptions which have long been applied to the condition commonly known as pylorospasm. To date, my own observations on this subject have been entirely clinical. They have been reinforced, so to speak, by the physiologic and pharmacologic findings of others.

RELATION BETWEEN "PYLOROSPASM" AND CONGENITAL HYPERTROPHIC PYLORIC STENOSIS

In some of our best textbooks on pediatrics, pylorospasm is considered secondarily in the discussion of congenital hypertrophic pyloric stenosis. The good results of surgery in the latter condition, and the opportunity for study of such cases on the operating table, may well be held responsible for the tendency to regard pylorospasm as a localized phenomenon, strictly confined to the pylorus, and often associated with organic hypertrophy. Such local spasm, plus increasing pyloric induration, has been advanced by many as the reason why infants with hypertrophic pyloric stenosis often do not begin to vomit until they reach the age of 1 week or more.

Now, from the mass of evidence at hand, one cannot escape the conclusion that congenital hypertrophic pyloric stenosis is a definite entity,[1] due to an underlying congenital malformation, frequently requiring surgical intervention. In a study of experimental pyloric stenosis (stenosis being produced by injection of paraffin into the walls of the pylorus), Tumpeer and Bernstein[2] state that because snakelike contraction waves are seen passing over the pyloric tumor on operation, some observers attribute the hypertrophy to this constant activity. Experimental evidence is given indicating that these contractions are caused by the tumor itself; and the important observation is made that spasm associated with the pyloric tumor of infancy is not affected by atropin.

It would be idle to dispute those who maintain that local spasm may play a part in producing the clinical picture which these cases

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* From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital.

[1] Holt, L. E.: Hypertrophic Stenosis, J. A. M. A. **68**:1517 (May 19) 1917.

[2] Tumpeer, I. H., and Bernstein, M. A.: Experimental Pyloric Stenosis, Am. J. Dis. Child. **24**:306 (Oct.) 1922.

present.[3] My object in mentioning this point is to emphasize that, as might be expected, it often causes confusion in the diagnosis of the purely functional type of expulsive vomiting, with the result that many infants have been subjected to operation who might have been cured by medical means.

Now, I have raised this question of surgical treatment early, because it is essential to the proper classification of the cases, i. e., organic and functional. It is incumbent on us, as advocates of medical treatment of infants with such motor gastro-intestinal disturbances, to explain our failures to the surgeons. After that, we may properly discuss the physiology and pharmacology of our successes. Insufficient dosage of atropin, neglect to carry out lavage or to feed thick cereal—any or all of these excellent reasons for failure of medical treatment will not justify our overlooking the fact that certain patients cannot be cured without operation. I have seen, as others have seen, patients with persistent projectile vomiting and rapid loss of weight given atropin in ample dosage, lavaged,[1] gavaged, and given thick cereal (Sauer[4]) with no resulting improvement, until operation was performed. Such cases exist because of the presence at the pylorus of a hard mass of tissue quite beyond the influence of anything except the knife. That such masses could form during the first week of life, without having begun in utero, seems inconceivable: we must concede the congenital malformation. Moreover, it is impossible to substantiate the contention that such firm, almost cartilaginous bands can be due to the activity of the vagus, even granting that this nerve supplies the pylorus.[5] The stomach and many feet of intestine are also supplied by the vagus; and why all the hyperactivity should be confined to that particular inch at the pylorus is difficult to see. Finally, when we come to consider the effect of administration of atropin, a general vagoplegic, we have an added argument against the theory of Haas that "pyloric stenosis is only an advanced degree of pylorospasm."[3] I think it safe to say that when a patient resists proper medical treatment he is suffering from that congenital malformation properly called congenital hypertrophic pyloric stenosis.

MOTOR DISTURBANCES OF FUNCTIONAL ORIGIN

If we can explain our failures on the basis of organic malformation, it is no less important to give an account of the successes of medical treatment. So well do clinical observations accord with physiologic and pharmacologic studies, that therapy in these conditions may now be said to have a rational basis, as etiologic factors have more and more been brought to light.

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[3] Haas, S. V.: Congenital Hypertrophic Pyloric Stenosis and Its Treatment by Atropin, J. A. M. A. **79**:1314 (Oct. 14) 1922.

[4] Sauer, L. W.: Arch. Pediat. **35**:385 (July) 1918; Pyloric Stenosis, Am. J. Dis. Child. **22**:166 (Aug.) 1921.

[5] There is still some dispute about this point. Compare Salomon, A.: Monatschr. f. Kinderh. **24**:75 (Oct.) 1922.

Physiologic Considerations.—Langley [6] has classified the autonomic or involuntary nervous system thus: A. Parasympathetic: (1) tectal, (2) bulbosacral; B. Sympathetic. The enteric plexuses of Meissner and Auerbach, he classifies separately as the *enteric system,* because of the lack of proof of their central connection, and because of their very distinct histologic structure. With this system, as with that division of the parasympathetic called the *bulbar autonomic,* we are directly concerned. The bulbar autonomic supplies almost exclusively the parts developed from, or in connection with, the primitive alimentary tract: the mucous membrane of the mouth, nose and pharynx, with lachrymal and salivary glands; the esophagus, stomach, liver, pancreas, small intestine, lungs and heart, and in some animals the upper part of the large intestine. The *sacral autonomic* supplies the lower part of the large intestine, the bladder and the genitalia.

There is still some uncertainty as to the exact manner in which the nervous mechanism controlling normal gastric and intestinal peristalsis is kept in a state of balance. In the mass of work done on the subject, there is, however, nothing to discredit the theory of dual innervation. Stimulation of the parasympathetic or vagus, as is well known, will cause a definite increase in gastric and intestinal peristalsis, whether such stimulation is by electricity or by such parasympathetic drugs as pilocarpin, muscarin, arecolin, physostigmin and cholin (Langley). Stimulation of the opposing (sympathetic) mechanism, as for example by the sympathetic drug (and secretion) epinephrin, has an inhibitory effect.[7]

Bearing in mind the admonition of Alvarez [8] "not to talk with certainty about what the splanchnics and vagi will do," we may assume that the enteric plexuses are capable of maintaining normal intestinal

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6. Langley, J. N.: The Autonomic Nervous System, Cambridge, 1921.

7. Howell, W. H.: Physiology, Ed. 8, Philadelphia, W. B. Saunders Company, 1921, p. 725. How complicated a phenomenon normal peristalsis has been found to be is evident from a consideration of: Cannon, W. B.: Am. J. Physiol. **6**:251, 1902. Wheelon, Homer, and Thomas, J. E.: J. Lab. & Clin. Med. **6**:124 (Dec.) 1920; Am. J. Physiol. **59**:72 (Feb.) 1922. Wheelon, Homer: Duodenal Motility, J. A. M. A. **80**:615 (March 3) 1923. Alvarez, W. C.: Gastric Peristalsis, J. A. M. A. **79**:1281 (Oct. 14) 1922. Magnus: Arch. f. d. ges. Physiol. **102**:515, 1904; **103**:525, 1905, quoted by Sollmann, T.: Physiol. Rev. **2**:479 (Oct.) 1922. Gunn and Underhill: Quart. J. Exper. Physiol. **8**:275, 1914.

8. Alvarez, W. C., in discussion of Barber, W. H.: Enteroparesis, J. A. M. A. **79**:1825-1828 (Nov. 25) 1922.

movements, and that preponderance of vagal or of sympathetic stimuli will increase or inhibit such movements, respectively.

The sympathetic hormone, the substance maintaining normal sympathetic tonus, is epinephrin, secreted by the chromaffin system. There is now little doubt that a parasympathetic hormone exists in cholin, a less understood but most important substance whose principal action is vasodilator, with secondarily resulting fall of blood pressure. As Langley says, pilocarpin is the most familiar parasympathetic stimulant, but the action of cholin, since it is formed in the body, is more important.[9] "It is clear that if excessive production of cholin or of epinephrin occurs, it will cause a whole group of symptoms similar in the main to those caused by the parasympathetic or the sympathetic nerves."

Conversely, an insufficiency of either substance might be expected to produce symptoms referable to excessive production of its opposite. Thus, in Addison's disease, with diminished epinephrin production, we find symptoms of excessive vagus activity, including in the later stages painful vomiting, eructations, hiccup and occasional diarrhea, constipation being commoner in the earlier stages.[10]

Etiologic Considerations.—Further studies on the formation and activity of cholin may be expected to throw more light on the etiology of vagus predominance, the same factor being in all probability responsible for the clinical condition variously known as vagotonia,[11] autonomic imbalance,[12] the hypertonus of infancy [13] and *gastronévrose émétisante*,[14] not to mention the misleading term pylorospasm, which has been in common use for so long.

Functional motor disturbances of the gastro-intestinal tract, of such importance in infancy, may also be found in certain conditions of later life. Among these, we may consider the cyclic vomiting of later childhood and the hypersthenic gastric diathesis [15] of adults. Here, the gastric crises [11] of tabetics should be mentioned, due in all probability to parasympathetic involvement in neurosyphilis; also lead colic, the symptoms of which readily respond to administration of atropin.[3]

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9. An interesting study of cholin is that of Hunt, Reid: Am. J. Physiol. **45**:197-231 (Feb.) 1918.

10. Dock, George, in Osler and McCrae: Modern Medicine, Ed. 2, Philadelphia, Lea and Febiger, 1915, p. 777.

11. Eppinger, H., and Hess, E.: Nerv. & Ment. Dis., Monograph, Series No. 20, New York, 1915.

12. Lieb, C. C.; Hyman, H. T., and Kessel, L.: Exophthalmic Goiter and the Involuntary Nervous System, J. A. M. A. **79**:1099 (Sept. 30) 1922.

13. Haas, S. V.: Hypertonic Infant, Am. J. Dis. Child. **15**:323 (May) 1918.

14. Lemaire, H., and Olivier: Nourrisson **10**:305 (Sept.) 1922.

15. Hurst, A. F.: Lancet **2**:1369 (Dec. 30) 1922.

As described by Kessel, Lieb and Hyman,[16] the syndrome of autonomic imbalance, including such symptoms as tachycardia, tremor, exophthalmos, sweating, asthenia and diarrhea, may be and often is mistaken for hyperthyroidism. In the presence of normal basal metabolism, they consider that hyperthyroidism is not a factor in such cases, that the autonomic imbalance is much more likely to precede than to follow thyrotoxicosis. There is clearly no reason to implicate the thyroid as a causative factor in infantile cases.

Tetany.—According to Lemaire and Olivier,[14] contracture of smooth muscles in tetany is now an accepted fact. They report four infants with habitual vomiting, whose ages at onset ranged from 17 days to 6 months—all with clinical symptoms of pylorospasm, plus those of tetany, with no improvement until calcium chlorid was given. Certain other infants with habitual vomiting, without signs of tetany, were not helped by the calcium chlorid. Whether the vigorous motor reaction of the small intestine following the intravenous injection of sodium bicarbonate in dogs [17] is due to smooth-muscle tetany from alkalosis may still be considered open to question.[18] King and Church found that, in some cases, such reaction was diminished by administration of atropin, and in others it was not. Administration of epinephrin temporarily abolished it.

Protein Sensitization.—Since the popularization of cutaneous sensitization tests, such conditions as cyclic vomiting, the exudative diathesis and also abdominal pain alone [19] have been added to the list of conditions attributed to sensitivity to foreign protein. It is by no means unreasonable to suppose that such sensitivity can, in some cases, result in autonomic imbalance which, in severe reactions, might produce vomiting and diarrhea, such as we see in shocked dogs, associated with urticaria, etc., due to the ingestion of an offending protein. Such reaction in milder degree, however, could take the form of "peristaltic unrest." In a limited number of cases, there is unquestionably a connection between protein sensitivity, the exudative diathesis and autonomic imbalance. Two of my own cases (Cases 6 and 7) illustrate how infantile eczema and vagogenic gastro-enterospasm may exist together, and in one of these (Case 7), there was definite sensitivity to several proteins.

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[16] Kessel, Leo; Lieb, C. C., and Hyman, H. T.: Exophthalmic Goiter and the Involuntary Nervous System, J. A. M. A. **79**:1213 (Oct. 7) 1922.

[17] King, C. E., and Church, J. G.: Am. J. Physiol. **62**:459 (Nov.) 1922.

[18] The Alleged Relation Between Alkalosis and Tetany, editorial, J. A. M. A. **79**:2232 (Dec. 30) 1922.

[19] Duke, W. W.: Food Allergy as a Cause of Abdominal Pain, Arch. Int. Med. **28**:151 (Aug. 15) 1921. Shannon, W. R.: Neuropathic Manifestations as a Result of Anaphylactic Reaction to Foods Contained in Dietary, Am. J. Dis. Child. **24**:89 (July) 1922.

Parenteral Infection.—Finally, there is a further factor in the etiology of infantile gastro-enterospasm to which sufficient importance has not been attached; namely, parenteral infection. It is a matter of common experience among pediatricians that, during infancy, an acute infection, such, for example, as otitis or pyelitis, may produce vomiting and diarrhea of severity out of all proportion to the amount of infective material which directly enters the alimentary tract. Such upsets, due not to direct irritation of the alimentary mucosa, but to outside infection, should be considered vagogenic, though just how the infection so stimulates the vagus is still a matter of conjecture. Attempts to prove by skin tests that there is sensitization to the bacterial protein have been disappointing. For the present, we shall have to resort to the old generality "toxic irritation" of the vagus, as the most nearly adequate explanation.[20]

CLINICAL OBSERVATIONS

In discussing the paper by Sauer et al.[21] on gastric findings in older children with anorexia, I called attention to the fact that certain of their remarks on the relation of habitus,[22] gastric motility and appetite were applicable to motor abnormalities in infancy. I emphasized at the time that when there is pylorospasm there is also enterospasm, which hurries the food through the intestine, thus causing these infants to require more food than normal infants of the same weight and age (a mechanical rather than a metabolic hunger). Haas writes: "The chief symptoms are those of muscle spasm. . . . Colic, visible peristalsis, both gastric and intestinal, constipation,[23] vomiting, sleeplessness and constant crying make up the picture, to which is added in some cases instability of the vasomotor system as shown by cyanosis of the circumoral region, cold, clammy hands and feet, subnormal temperature and inability to make progress on any form of feeding."

Essentially the same symptoms are described by Shawkey,[24] who raises the very natural question "Why do such infants not have diarrhea?" His answer is that the anal sphincters, as shown by digital examination, share in the hypertonicity, being so firmly contracted as to prevent the passage of stools, though these are soft when finally passed. He cites cases in which constipation has been definitely and promptly relieved by atropin, with return of the constipation when the drug was discontinued. Haas [13] also includes this type of constipation in his description of the hypertonic infant.

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[20] Reference should be made at this point to a number of articles bearing on the subjects we have discussed: Kay, W. E.: A Study of One Hundred Cases Diagnosed as Hyperthyroidism, J. A. M. A. **79**:2149 (Dec. 23) 1922. Held, I. W., and Roemer, J.: Gastrospasm, Am. J. Med. Sc. **164**:188 (Aug.) 1922. Finney, J. M. T., and Friedenwald, J.: Pylorospasm in Adults, Am. J. M. Sc. **162**:469 (Oct.) 1921. (They found that in adults, the purely neurotic variety of pylorospasm was much less common than the irritative and reflex varieties.) Barber, W. H.: Footnote 8.

[21] Sauer, L. W.; Minsk, L. D., and Alexander, W. G.: Gastric Findings in Children with Anorexia, J. A. M. A. **79**:184, (July 15) 1922.

[22] Mills, R. W.: Am. J. Roentgenol. **4**:155 (April) 1917.

[23] That diarrhea may occur frequently is shown by a number of the cases reported later.

[24] Shawkey, A.. A.: West Virginia Med. Monthly **17**:201 (Dec.) 1922.

Now I have implied that diarrhea is rather more to be expected than constipation, emphasizing the similarity between the alimentary hyperactivity of infancy and the neurogenic diarrhea of later life. Shawkey's question as to why the infants we are discussing do not have diarrhea may be answered in part by saying that many of them do, as is illustrated by cases herewith reported. I feel sure that others will be able to report similar cases. By diarrhea, I do not mean the scanty, mucoid, frequent stools which barely stain the diaper, properly described as starvation stools. I mean true diarrhea, with copious, watery, green stools, which may appear before or after the onset of projectile vomiting (Cases 1 and 2). I do not intend to imply, however, that constipation is uncommon in enterospastic infants. Firm contraction of the anal sphincters is, nevertheless, an inadequate explanation of it. It will be remembered [25] that the parasympathetic innervation of the lower part of the large intestine is derived from the sacral autonomic. Now, autonomic drugs, such as atropin, have decidedly different effects on different divisions of the autonomic system, such effects varying with the dosage and with the individual patient or animal. Similarly, with bodily secretions: there is both pharmacologic and clinical evidence that hyperactivity of stomach and small intestine, or of the latter alone, does not necessarily involve the large intestine. Consequently, a stool may be hurried through the small intestine, to remain for a long time in the descending colon and sigmoid. In this is a plausible explanation for the green but hard stools which are not infrequently seen, the color being due to unchanged bile pigments, the firm consistency to extraction of water in the colon and sigmoid. Sphincter contraction may, of course, be an additional factor.

EFFECT OF ATROPIN ON INFANTILE GASTRO-ENTEROSPASM

Reports of results of atropin therapy vary in enthusiasm all the way from that of Haas, who considers the drug a specific, to that of Levy,[26] who does not think it necessary, largely because of his good results with thick cereal feeding. The great majority of observers—I shall not attempt a complete review—concede that administration of atropin is at least as important as lavage and thick cereal feeding. To my mind, it is by far the most important, and usually the only essential, medical measure. It has, besides, a diagnostic value of prime importance. Often it is impossible to differentiate between organic and spastic obstruction, without resort to the therapeutic test.

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[25] 25. Langley, J. N.: Footnote 6. Sollmann, Torald: Physiol. Rev. **2**:479 (Oct.) 1922.

[26] 26. Levy, D. J.: J. Michigan M. Soc. **21**:166, 1922.

Using as subjects six healthy infants from 3 weeks to 8 months of age, Salomon [5] found that atropin in a dosage of from 2 to 3 drops of a 1 : 1,000 solution retarded the emptying time of the stomach, food residue being found as long as five hours after feeding. After twenty-four hours of atropin therapy, he found no diminution of hydrochloric acid secretion, nor any alteration of hydrogen ion concentration.[27] Fluoroscopy revealed a relaxation of gastric tonus, dilatation of the stomach, slowing of peristalsis and increased shallowness of antral movements. No influence on the pylorus in the way of relaxation was noted,[28] which would seem to indicate that parasympathetic innervation of the pylorus may be of but little significance. The observation, however, awaits confirmation by others; and for the present, we may accept the view [2] that atropin does not exert a selective action on the pylorus, but paralyzes the vagus endings with depression of all gastric peristalsis, and, with regard to the small intestine, prevents vagus predominance, permitting the plexuses of Meissner and Auerbach to carry on normal peristalsis.

Practical Points in Administration of Atropin to Young Infants.—1. The solution should not be used when it is more than 2 weeks old. 2. A good prescription is:

	Gm. or C.c.	
℞ Atropin sulphate............	|03	gr. ss
Distilled water..............	30|	fl ℥ i

One minim thus contains one nine hundred and sixtieth grain of atropin. It should be given in a little water, fifteen minutes before each feeding, to permit the atropin to take effect before ingestion of food. If no improvement results, the dose may be gradually increased till three or even five nine hundred and sixtieth grain is given before each of five feedings. (The four-hour interval is preferable, to allow maximum rest for the alimentary tract.)

3. The Barnes, or some other accurate minim-dropper, should be used. The solution may be placed in about half a teaspoonful of water,

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[27] Contrast results of B. C. Lockwood and H. G. Chamberlin (Effect of Atropin on Gastric Function as Measured by Fractional Analysis, Arch. Int. Med. **30**:806 [Dec.] 1922, who found (in adults) that atropin in maximum clinical dosage depresses both free and total acidity 30 per cent. Their results differed further from those of Salomon in that they found bile in the gastric contents oftener after atropin therapy because of the greater pyloric relaxation.

[28] Similar results were obtained by Lasch (Klin. Wchnschr. **1**:840 [April] 1922) and by Otvös (Arch. f. klin. Med. **136**:58 [April] 1921).

and given through an empty nipple. If any is lost, the mother should not try to "make it up" by giving more.

4. Unless the flushing which may follow a dose is extremely marked, no alarm need be felt. The next dose of the same amount may produce no flushing at all. However, definite flushing is evidence of sufficient dosage. Dry-mouth is not a reliable sign in early infancy.

5. Failure of pupils to react to light is one of the latest signs of atropinization; when it appears, the dose should be reduced.

6. After the baby's condition has been satisfactory for from four to six weeks, an attempt at gradual reduction of the dose should be made.

Special Indications for Feeding Thick Cereal.—Though I believe that atropin will cure all functional cases presenting, among other symptoms, those of pyloric obstruction, and that patients not thus relieved are suffering from organic stenosis, there are, nevertheless, mild degrees of the latter which, though unaffected by atropin,[2] are amenable to medical treatment. It is in such cases that thick cereal feeding is of the greatest value. Unavailing in extreme organic stenosis, unnecessary in functional gastro-enterospasm, it may often permit a child with moderate or even marked stenosis to gain or at least to hold its weight till the condition is outgrown.

It is not the object of this paper to report, from a large series of cases, the proportion responding to the different forms of treatment. With one exception, I shall present only cases illustrative of the vagogenic gastro-enterospasm which has been discussed.

REPORT OF CASES

Case 1.—P. W., a girl, whose family history was of considerable interest, and who resembled the mother, gave a negative history on the father's side, except that "they are all high-strung." The mother's father and two sisters and the mother herself were subject to hunger-pains and unpleasant sensations if meals were long delayed. The mother's mother was free from autonomic symptoms except marked hyperhidrosis. The mother and two sisters had low blood pressure (from 90 to 100 mm. of mercury) and were very easily tired, though energetic. The mother and her younger sister were subject to attacks of "unexplainable diarrhea," with abdominal cramps. There was no evidence of a high metabolic rate. The mother was subject to headaches and to hyperhidrosis.

The patient was born at term, and delivery was normal. No gain was made during the first ten days of life. There were from three to six watery stools a day during the first month, and occasionally eight or nine. The bowels usually moved after each feeding, with additional movements between feedings. She was given both breasts for a total of twenty minutes every four hours, to insure a maximum of breast milk with a minimum of bowel stimulation. At the age of 2 weeks, she began to gain from 7 to 8 ounces (198 to 226 gm.) a week. However, as she showed signs of hunger, supplementary feeding with a milk-water-and-sugar formula was begun, and eagerly taken, with neither increase nor decrease in the number of stools.

As the age of 1 month, projectile vomiting began, the diarrhea continuing. On the first day of vomiting, the baby expelled all of three feedings immediately after taking them. She screamed almost constantly; the act of feeding apparently causing great pain, and being followed by the passage of loose stools with much gas. Gastric and intestinal peristalsis were now visible. She was at once given ⅙₆₀ grain, of atropin fifteen minutes before each feeding. This was obtained from a small local drug store. No improvement resulted during the next two days. A fresh supply of atropin was bought from a more active prescription pharmacy, and after the first three doses of this preparation, the improvement in the baby's behavior was remarkable. She vomited only a few times afterward, and the number of stools was reduced from six or eight a day to two or three. While on atropin, she was more fussy than the normal baby, usually crying from 6 to 10 p. m., though taking plenty of food and gaining rapidly. The atropin, though fresh, had to be increased to $\frac{1}{480}$ grain before feeding. Only occasional flushing resulted.

Several attempts to discontinue the atropin were made, one being followed by diarrhea so severe as to require starvation and speedy resumption of the drug. Other attempts at discontinuance were followed by extreme fretfulness, and in one instance by vomiting. Finally, at the age of 8 months, atropin was discontinued, without return of symptoms. At the age of 18 months, the appetite is still voracious, and the bowels tend much more to looseness than to constipation. The weight is normal.[29]

Case 2.—D. D., girl, first seen at the age of 3 weeks, had had frequent stools (nine or ten daily) since birth. Nursing was painful. The baby screamed most of the time, except between 11 p. m. and 6 a. m. Projectile vomiting began at the age of 1 month. There was visible peristalsis. Vomiting occurred five times during the week. Both vomiting and diarrhea were checked promptly by atropin, $\frac{1}{480}$ grain, given before each feeding (five feedings a day). At the age of 6 months, the patient still requires the drug. She is "fretful while taking it but frantic without it."

Case 3.—R. G., boy, first seen at age of 4 weeks, had made no gain since birth. Projectile vomiting had occurred after each feeding, since birth. There were two constipated stools a day, green when passed. The baby was very fretful, especially when nursed. There was visible peristalsis. He was allowed to continue nursing every three hours, and was given $\frac{1}{960}$ grain of atropin fifteen minutes before each nursing. The number of stools remained the same, but they were no longer green. The patient gained weight very rapidly and was no longer fretful. The amount of atropin was gradually decreased at age of 3 months, and administration was not resumed.

Case 4.—A. W., girl, first seen at age of 5 weeks, was an example of the mismanagement to which such patients are often subjected, having been nursed very irregularly, treated by "any number of physicians," and given every known cathartic and other drugs in profusion. She was quite constipated, though the consistency and color of the stools were normal. She made a good recovery on atropin. As in Cases 1 and 2, this baby had to be weaned early, lack of rest for the mother being the main factor in diminishing the supply of breast milk.

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[29] One cannot predict the length of time during which atropin will be required in these cases. I know of one patient who required it until the age of 15 months. It is unusual, however, to have to give it longer than from one month to three months. The fact that the condition may occur in adults has been referred to at some length. The mother of the baby in Case 1 was relieved by it, but required such large doses that great inconvenience from visual impairment resulted. The idiopathic pylorospasm of adults is probably due to autonomic imbalance, the secondary pylorospasm being due to such local condition as gallstones and appendicitis. (Compare Finney and Friedenwald: Footnote 20; also Einhorn and Scholz: Med. Rec. **98**:883 (Nov. 27) 1920.

CASE 5.—A. N., first seen at the age of 4 months, had been weaned two weeks previously and was given condensed milk. He had always "fought the breast," and was a dirty, ill-kept, athreptic baby (hospital case.) Peristaltic waves were seen, passing from left to right (a sign which may often be discounted in an athreptic baby with diarrhea). Atropin therapy, plus proper feeding, resulted in such prompt improvement that the drug was discontinued in three days and was not resumed. This was one of a considerable number of cases in which it could not be determined whether the atropin or the change to proper feeding was the principal factor in effecting cure.

CASE 6.—R. McC., boy, first seen at the age of 4 weeks, weighed at birth 6 pounds and 14 ounces, (3,118.50 gm.), and at 4 weeks, 6 pounds and 9 ounces (2,976.75 gm.). Delivery (instrumental) was difficult; and the baby was too weak to nurse. The breast pump was used in vain. The physician gave a powdered milk formula of proper strength, but whenever the baby took a sufficient quantity, diarrhea resulted, necessitating periods of starvation and administration of rice water. When first seen, the baby was passing about six greenish, watery stools a day. He was excessively fretful, with breath-holding attacks of alarming duration. The buttocks were quite "raw" from the irritating stools. There was moderate general glandular enlargement. The spleen was never palpable.

The baby improved somewhat during the first three weeks on a whole milk modification. Then a marked facial eczema appeared; the diarrhea became worse, and he was given a lactic-milk-dextrimaltose formula. He did fairly well, the number of stools decreasing to two or three a day; but the condition of the buttocks remained the same, and the gain was unsatisfactory, the weight at 10 weeks being only 7 pounds and 8 ounces (3,402 gm.). At that age, he began vomiting after each feeding, the vomiting being only moderately forceful. This condition cleared up in four days, with no change in treatment. At the age of 12 weeks, the eczema was very marked. The baby was then getting 63 calories per pound of body weight, without diarrhea or vomiting. In view of the hypothreptic condition, it was considered more important to give a high calory diet than to underfeed him, because of his eczema.

Sensitization tests for milk proteins, the only ones he was then receiving, were negative, as was also the Pirquet test. One week later, the vomiting and diarrhea returned. The weight remained stationary, and there was increasing fretfulness. At 13 weeks, the vomiting, which had been more like marked regurgitation, became projectile, entire feedings being vomited once or more often every day. After a futile attempt to check the vomiting and diarrhea by the use of skimmed lactic-acid milk, atropin was resorted to. The dose was rapidly increased (in four days) to 1/480 grain before each of the five feedings given. In spite of the diarrhea at that time, the feeding was increased to whole lactic-acid milk, 24 ounces (532 c.c.); water, 3 ounces (89 c.c.); 50 per cent. corn (Karo) syrup, 3 ounces (89 c.c.). The five feedings, 6 ounces (178 c.c.) each, gave about 70 calories for each pound of body weight. The atropin was depended on to check the diarrhea. As for the diet itself, such a formula, though very concentrated, has repeatedly caused constipation in ordinary cases of infantile diarrhea, i. e. those due to fermentation and local irritation. Within four days, the vomiting had stopped; the stools were reduced to two a day; the irritated buttocks were greatly improved, and the baby seemed better in every way. Except for pneumonia and otitis at the present writing, his subsequent course has been satisfactory.

This, then, is a case combining the exudative diathesis with alimentary motor disturbance of a character more enterospastic than gastrospastic, in which administration of atropin proved practically the only efficient therapy.

Case 7.—T. L., boy, first seen at the age of 3 weeks, the chief complaints being diarrhea, vomiting and fretfulness, was breast fed every four hours, and gained rapidly in spite of these complaints. He always had five or six green watery stools a day. The bowels always moved during or immediately after nursing, which seemed to cause great pain. A severe facial eczema appeared at the age of 6 weeks. No sensitization tests were performed, but the mother was told to stop eating eggs (Shannon). In a week, the eczema had greatly improved, only to return two weeks later, at the age of 3½ months. At this time, because of constant fretfulness, painful nursing, continued diarrhea and increasing regurgitation, atropin was started. Both the diarrhea and vomiting promptly subsided, and the baby quieted down within a week. At the age of 4 months, the eczema was so severe that sensitization tests were made. Pronounced reactions to wheat, egg white and beef serum were obtained. The mother carefully obeyed the indicated dietetic instructions; and the eczema was practically well in two weeks. The baby is now 15 months old. Atropin was discontinued after one month. The offending proteins were gradually added to the mother's dietary without return of the baby's eczema, which was most severe at onset.

Sensitization tests in a number of other cases of eczema in breast-fed babies have been disappointing, in contrast to the successful result in this case.

Case 8.—R. W., girl, first seen at the age of 3 weeks, had suffered from projectile vomiting since the age of 3 days. There was rapid loss of weight; starvation stools, and visible gastric peristalsis. She was given an adequate course of atropin therapy without benefit. Thick cereal feeding resulted in the prompt cessation of symptoms and in rapid gain in weight.

As pointed out in the preceding discussion, this case was in all probability one of moderate organic stenosis, instead of functional gastro-enterospasm.

CONCLUSIONS

1. Congenital hypertrophic pyloric stenosis is a congenital malformation, not related to pylorospasm.

2. The term pylorospasm should be abandoned in favor of the term gastro-enterospasm.

3. Gastro-enterospasm is a manifestation of autonomic imbalance which may occur in adults as well as in children. This is not related to thyrotoxicosis, but may be due to excessive production of cholin. Tetany, protein sensitization, the exudative diathesis and parenteral infection may be associated etiologically with gastro-enterospasm.

4. The principal clinical manifestations of this condition are (*a*) great fretfulness, aggravated by feeding, perhaps with failure to gain during the first weeks of life; (*b*) projectile vomiting, with diarrhea or constipation, with or without visible gastric or intestinal peristalsis; (c) absence of tumor at the pylorus, and (*d*) ready response to atropin therapy.

5. Atropin, if sufficiently fresh, and if given in adequate dosage, is a specific for vagogenic gastro-enterospasm.

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A PROOF OF THE REGULATORY INFLUENCE OF COD LIVER OIL ON CALCIUM AND PHOSPHORUS METABOLISM *

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The demonstration of the preventive and curative action of radiant energy and of the organic factor contained in cod liver oil in rickets has made studies of the action of these therapeutic agents of fundamental importance. At the present time, investigations indicate that the salts chiefly concerned in the disturbance in mineral metabolism which constitutes rickets are those of calcium and phosphorus. The experiments reported in this paper, begun in January, 1922, were planned to demonstrate whether or not cod liver oil exerts a regulatory influence on the calcium and phosphorus metabolism of rats.

Before describing the experiments, it seems advisable to point out certain facts recently discovered concerning the calcium and inorganic phosphorus content of the blood.

The concentration of calcium in the blood serum is apparently never above a value believed in normal children to be between 10.0 and 11.0 mg. per hundred cubic centimeters of serum, and in adults between 9.0 and 10.5 mg. per hundred cubic centimeters.[1] Kramer, Tisdall and Howland [2] state that the figures for the calcium concentration "are remarkably constant not only for the same animal but for animals of different species." The administration of certain calcium salts by mouth to animals on ordinary diets has not resulted in an increase of calcium in the serum, and the hypodermic and intravenous administra-

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[1] Kramer, Benjamin; Tisdall, F. F., and Howland, John: Clinical Significance of Calcium Concentration in Serum of Children and Possible Errors in the Determination, Am. J. Dis. Child. **22**:560-564 (Dec.) 1921. Halverson, J. O.; Mohler, H. K., and Bergeim, O.: J. Biol. Chem. **32**:171 (Nov.) 1917.

[2] Kramer, Tisdall and Howland: Footnote 1, first refernce.

tion has produced only a temporarily rise.[3] If, however, the calcium concentration in the serum is low, it may be raised by the administration of certain calcium salts. A low blood serum calcium is constantly found in infantile tetany,[4] and frequently in rickets without manifest tetany [5] and in certain cases of nephritis.[1] It is not known to what extent calcium in the blood is ionized.

The inorganic phosphorus of the blood serum in normal children, Howland and Kramer report, averages 5.4 mg. per hundred cubic centimeters of serum, with a minimum of 4.0 mg. and a maximum of 7.1 mg.[6] The inorganic phosphorus is increased directly after the ingestion of food.[7] It varies with the phosphate content of the diet and is possibly influenced by many other dietary factors.[8] Meigs, Blatherwick and Cary [9] summarize their work on the inorganic phosphorus of the plasma of cows thus: "The concentration of phosphatide and of inorganic phosphate in the plasma are highly variable. Both can be made to vary by changing the amount of phosphorus supplied with the rations, though the variations induced in this manner show themselves most markedly in the inorganic phosphate." The inorganic phosphorus is higher, according to Howland and Kramer,[10] in breastfed children (average, 6.1 mg.) than in artificially fed children (average, 5.1 mg.). In rickets, the inorganic phosphorus in the serum is usually low; [11] and in certain cases of nephritis, high.[12] Certain

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3. Clark, G. W.: J. Biol. Chem. **43**:89 (Aug.) 1920. Dennis, W., and Minot, A. S.: J. Biol. Chem. **41**:357 (March) 1920. Heubner and Rona: Biochem. Ztschr. **93**:187, 1919. Brown, Alan; MacLachlan, Ida F, and Simpson, Roy: Effect of Intravenous Injection of Calcium in Tetany and the Influence of Cod Liver Oil and Phosphorus in the Retention of Calcium in the Blood, Am. J. Dis. Child. **19**:413 (June) 1920.

4. Howland, John, and Marriott, W.: Quart. J. Med. **11**:289 (July) 1918. Kramer, Benjamin; Tisdall, F. F., and Howland, John: Infantile Tetany, Am. J. Dis. Child. **22**:431-437 (Nov.) 1921. György, P.: Jahrb. f. Kinderh. **49**:1, 1922.

5. György, P.: Footnote 4, third reference. Howland, John, and Kramer, Benjamin: Calcium and Phosphorus in Serum in Relation to Rickets, Am. J. Dis. Child. **22**:105-119 (Aug.) 1921. Iversen, P., and Lenstrup, E.: Forhandlingerne ved første Nordiske Kongres for Paediatri, 1920 (cited by Howland and Kramer). Findlay, L.; Paton, D. N., and Sharpe, J. S.: Quart. J. Med. **14**:352 (July) 1921.

6. Howland and Kramer (Bull. Johns Hopkins Hosp. **33**:313 [Sept.] 1922) state that the normal value of the inorganic phosphorus in the blood serum of rats is between 7.0 and 8.5 mg. See also: Howland and Kramer: Footnote 5, second reference.

7. Greenwald, I., cited in a review: The Biochemistry of the Blood in Relation to Its Calcium and Phosphate Content, Med. Sc. **6**:470-482, 1922.

8. Meigs, E. B.; Blatherwick, N. R., and Cary, C. A.: J. Biol. Chem. **37**:1 (Jan.) 1919. Greenwald, I.: J. Biol. Chem. **21**:29, 1915.

9. Meigs, Blatherwick and Cary: Footnote 8, first reference.

10. Howland and Kramer: Footnote 5, second reference.

11. Footnote 5. Hess, A. F., and Unger, L. J.: Tr. Am. Pediat. Soc. **34**:208, 1922.

12. Greenwald: Footnote 8, second reference. Marriott, W. McK., and Howland, John: Phosphate Retention, Arch. Int. Med. **18**:708 (Nov.) 1916.

pathologic conditions, namely, granulating wounds[13] and healing fractures,[14] are accompanied by an increase in the inorganic blood phosphorus. In adults, the inorganic phosphorus is lower than in children.[10] The concentration of the inorganic phosphorus in the blood serum, therefore, is subject to wide variation, and a "normal" inorganic phosphorus level, as such, has been established only within considerable latitude. It seems best to speak of the "usual" value of the inorganic phosphorus rather than of the "normal" value.

EXPERIMENTAL DATA

For the study contemplated in this work, five experiments were performed. A basal[15] ration low in calcium, phosphorus and fat-soluble A was used. The variations desired in the calcium and inorganic phosphorus content of the rations to be used in the individual experiments were secured by adding to this basal diet different amounts of either calcium carbonate or disodium phosphate, or both. Five rations, therefore, were required, each differing from the others simply in its content of calcium and inorganic phosphorus.[16]

In each experiment, about sixteen rats, varying in age between 36 and 44 days, were used. The animals were kept on the ration chosen for a given experiment for thirty-five days. At the expiration of this period, one-half the animals were bled, and the calcium and inorganic phosphorus of the pooled blood serum was determined. The remaining rats in the group were kept on the same ration as before, but with the addition to it of 2 per cent. (by weight) of cod liver oil. At the expiration of ten days, these animals were bled and the calcium and inorganic phosphorus of their pooled blood serum were determined.

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[13] Eddy, W. H., and Heft, H. L.: J. Biol. Chem. **55**:12, 1923.

[14] Tisdall, F. F., and Harris, R. I.: Calcium and Phosphorus Metabolism in Patients with Fractures, **79**:884-887 (Sept. 9) 1922.

[15] As shown in Table 1, the rations used in the individual experiments were practically identical in their content of sodium chlorid, ground whole wheat, corn, gelatin and gluten flour. These constituents constituted the basal ration.

[16] The five rations as prepared were prescribed by Prof. E. V. McCollum, who characterized them (in a personal communication to the authors) as regards their calcium and phosphorus content, as follows: I, Low calcium-low phosphorus; II, Low calcium-moderate phosphorus; III, Low calcium-high phosphorus; IV, Optimum calcium-optimum phosphorus, and V, High calcium-low phosphorus. The calcium and inorganic phosphorus content of the diet which is optimum to ensure to the rat normal growth and reproduction is not accurately established; indeed, the problem is an exceedingly complex one, and probably a number of other factors beside actual quantities are of equal importance. So far as amounts are concerned, McCollum regards 0.60 and 0.45 per cent. for calcium and inorganic phosphorus, respectively, as amounts probably near those requisite. The ration used in Experiment IV closely fulfils these stipulations.

The animals were kept in roomlight in metal cages, which were suspended in racks so that there was opportunity for most of the excreta to drop beyond reach. No nesting material was provided.

The chemical examinations were made in each instance on the pooled serum from all the rats in a given group. The animals were bled under ether anesthesia by cutting the jugular vein (one or both) and the carotid artery (one or both), and allowing the blood to drop into a funnel and from thence into a centrifuge tube. In a few instances, the animals were anesthetized and decapitated, and the bodies bled into a funnel. The inorganic phosphorus of the serum was determined colorimetrically as the phosphomolybdate, titrated against a known standard. The general quantitative relations were those described by Briggs.[17] The calcium of the serum was precipitated directly as the oxalate (as suggested by Kramer and Tisdall[18]) and titrated against potassium permanganate.

Table 1.—*Summary of Data Regarding Experimental Diets*

Experiment	Wheat, Gm.	Maize, Gm.	Gelatin, Gm.	Wheat Gluten, Gm.	Dextrin, Gm.	NaCl, Gm.	$CaCO_3$, Gm.	NaH_2PO_4 $12 H_2O$, Gm.	Ca per 100 Gm. Diet, Gm.	P per 100 Gm. Diet, Gm.	Weight-Ratio Ca : P
I	33.00	33.0	15.0	15.0	3.0	1.0	...	....	0.01	0.29	1:29
II	35.15	33.0	15.0	15.0	...	1.0	...	0.85	0.01	0.38	1:38
III	33.45	33.0	15.0	15.0	...	1.0	...	2.55	0.007	0.59	1:81
IV	33.00	33.0	15.0	15.0	...	1.0	1.5	1.68	0.66	0.47	1:0.7
V	33.00	33.0	15.0	15.0	...	1.0	3.0	....	1.42	0.26	1:0.18

Table 2.—*Summary of Data Regarding Experimental Animals*

				Before Administration of Cod Liver Oil			After 2% Cod Liver Oil for 10 Days		
Experiment	No. of Rats	Average Age, Days	Days on Diet Before Cod Liver Oil	No. of Rats Bled and Killed	Ca*	P*	No. of Rats Bled and Killed	Ca*	P*
I	18	40	35	10	5.0	6.0	8	8.8	5.8
II	15	44	35	8	5.6	7.9	7	9.1	6.6
III	13	43	33	7	4.2	11.1	6	8.6	10.8
IV	20	43	35	10	7.6	6.6	10	9.0	5.5
V	14	36	35	8	10.1	1.3	6	10.7	6.0

* Ca and P determinations were made on the serum of pooled blood and are expressed in milligrams per hundred cubic centimeters of serum.

In Tables 1 and 2 are summarized the data from the experiments. These data are schematically shown in the accompanying chart. In Table 1 are given the constituents and calcium-inorganic phosphorus ratios of the diets used in the individual experiments. In Table 2 may be found the details of each experiment as regards the age and number of animals; the calcium and inorganic phosphorus concentration of the blood serum of some of the animals (number of animals given) after thirty-five days on the diet, and then in the blood serum of the remainder (number of animals given) after ten additional days on the diet with 2 per cent. cod liver oil added.

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[17] Briggs, A. P.: J. Biol. Chem. **53**:13 (July) 1922.

[18] Kramer, Benjamin, and Tisdall, F. F.: J. Biol. Chem. **47**:475 (Aug.) 1921.

The following summaries of the individual experiments bring out the striking influence of cod liver oil on the concentration in the blood serum of the calcium and inorganic phosphorus. Attention will also be called to certain other interesting data.

Experiment I. The ration used in this experiment contained only a trace of calcium and 0.29 per cent. of inorganic phosphorus—a diet deficient, therefore, in both calcium and inorganic phosphorus, particularly the former. This deficiency is reflected in the blood as shown in the analyses of the serum of the ten rats killed at the expiration of thirty-five days. The inorganic phosphorus was slightly lower than the "usual" value, and the calcium was reduced to 50 per cent. of the accepted normal amount. At necropsy the animals showed rickets. When the blood of the remaining animals, which had received cod liver oil for ten days, was examined, it was found that the inorganic phosphorus was unchanged and the calcium had increased 76 per cent.—to 8.8 mg., almost the normal value.

Experiment II. In this experiment also there was only a trace of calcium in the diet, but the inorganic phosphorus (0.38 per cent.) was nearer the "optimum" than in the ration used in Experiment I. The blood serum of the animals killed after thirty-five days showed a calcium concentration (5.6 mg.) which was almost the same as that found in the blood of the corresponding group in the preceding experiment. The inorganic phosphorus (7.9 mg.) was higher. Postmortem examinations revealed mild rickets. The influence of the administration of cod liver oil was the same as in Experiment I; i. e., there was no significant change in the inorganic phosphorus, and the calcium had increased 62 per cent.—to 9.1 mg., the normal value.

Experiment III. The ration used contained only a trace of calcium, but a great excess of inorganic phosphorus (0.6 per cent.), an amount probably considerably above the optimum. The results of this dietary as reflected in the blood serum of the animals at the end of thirty-five days is most striking, the calcium being low (4.2 mg.)—about 42 per cent. of the normal—and the inorganic phosphorus 11.1 mg., a value well above the usual.[19] Postmortem examination of these animals revealed marked rickets; the so-called low calcium rickets. After ten days of cod liver oil therapy, the inorganic phosphorus was unchanged and the calcium had increased about 100 per cent.—to 8.6 mg., almost the normal value.

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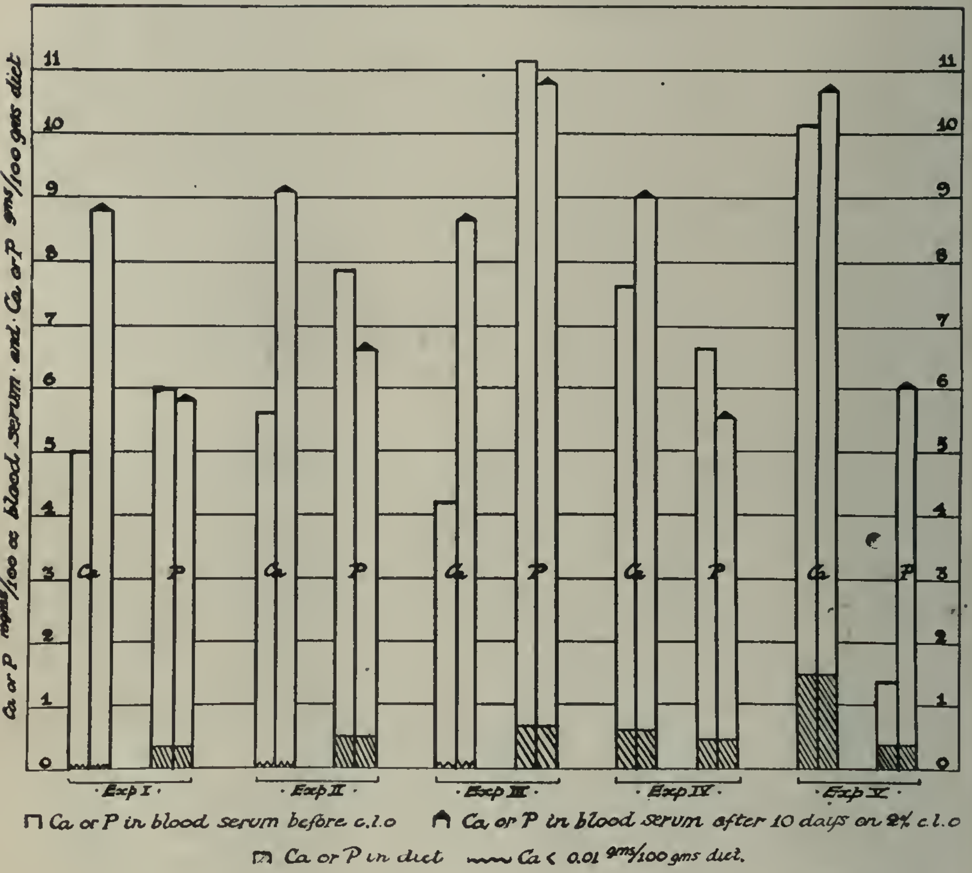
[19] There is, therefore, in these data, an excellent demonstration of the fact that the feeding of excessive amounts of the salts of phosphorus will force the level of the inorganic phosphorus in the blood serum beyond the value considered normal by Howland and Kramer (Bull. Johns Hopkins Hosp. **33**:313 [Sept.] 1922).

Experiment IV. Here the ration is probably about optimum in its content of calcium (0.66 per cent.) and inorganic phosphorus (0.47 per cent.). The calcium and inorganic phosphorus of the blood after thirty-five days was somewhat lower than the "usual" values. The addition of cod liver oil produced no striking change in the inorganic phosphorus or the calcium. At necropsy, the animals showed bones which did not differ greatly from the normal.



Calcium and phosphorus levels before and after ingestion of cod liver oil.

Experiment V. The diet used in this experiment regularly produces marked rickets of the so-called low phosphorus type. The ration contained an excess of calcium (1.42 per cent.) and a moiety of inorganic phosphorus (0.26 per cent.). The effect of this high calcium-phosphorus ratio on the blood serum after thirty-five days was shown in a high calcium concentration (10.1 mg.) and in an extremely low inorganic phosphorus (1.3 mg.). At necropsy, these animals showed the classic signs of rickets. When the blood serum of the remaining animals, which had received cod liver oil for ten days, was examined, it was found that the inorganic phosphorus had increased over 360 per cent.—to 6.0 mg.—and the calcium was unchanged.

COMMENT

Data similar to those presented in this paper have already been furnished by Howland and Kramer [20] as a result of their calcium and inorganic phosphorus determinations on the groups of rats used by McCollum, Simmonds, Shipley and Park in experiments on rickets. The variations in the calcium-phosphorus ratios in the diets used and the corresponding changes in the blood serum were not so great as in our experiments.

The experiments [21] presented here show that when radiant energy and the organic factor contained in cod liver oil are deficient, certain disproportions in the calcium and phosphorus of the diet produce corresponding disproportions in the concentration of these elements in the blood serum. These findings are in accord with investigations already referred to in this paper. They are emphasized here simply because the demonstration is unusually clear cut.

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[20] Kramer, Benjamin, and Howland, John: Bull. Johns Hopkins Hosp. **33**:313 (Sept.) 1922.

[21] The experiments are not free from the possibility that they yield data technically correct but susceptible to incorrect interpretation and correlation. The relationship of the salt concentration in the blood serum to the ingestion of food may have been such as to give values, particularly as regards the inorganic phosphorus, which were neither "normal" nor "usual." While this criticism is valid, it is not pertinent to the subject of inquiry in this experiment; namely, the determination not of standards but of relations under the influence of specific dietary ingredients. In order to maintain, as nearly as possible, constant relations, the bleeding of the rats in each experimental group was always begun at the same hour of the day.

The slight variation in the initial ages of the rats in the several experimental groups, as well as the added ten-day period of life of those animals receiving cod liver oil, brings forward the question of the variations with age of the concentration of inorganic salts in the blood serum. It was impossible to get animals of identical age in the required number. A certain period on the diet plus cod liver oil had to be chosen. Clear-cut healing effects of cod liver oil on human rickets are demonstrable in the blood serum in about ten days, and that interval accordingly was chosen for these experiments. It has not been shown that variations with age *per se* occur in the concentration of salts in the blood serum of rats. Such variations, however, may take place. In any case, the changes which may occur with variations in age in the calcium and inorganic phosphorus in the blood serum of animals, either on diets considered normal or on those defective in their salt content, are probably slight compared with those here attributed to the influence of cod liver oil.

The experiments demonstrate in a striking manner the regulatory power of cod liver oil on the calcium and phosphorus metabolism of the organism. The changes in the concentration of the calcium and inorganic phosphorus of the blood serum which occurred under the influence of cod liver oil were striking in degree. No less striking was the constancy with which the concentrations moved toward those found in the blood of healthy rats on ordinary diets. It is an extraordinary fact that a substance containing neither calcium nor phosphorus, when administered to an animal whose blood is deficient in these elements, should have the power to cause the calcium or the phosphorus, as the case may be, to rise to, or nearly to, the level commonly regarded as normal and thereby to establish the normal equilibrium. Cod liver oil has this extraordinary power.

Cod liver oil not only acts as a regulator of the calcium and phosphorus metabolism, but also permits the organism to operate with greatly increased economy. In the presence of calcium or phosphorus starvation, cod liver oil enables the animal to get along as if the calcium or the phosphorus were supplied in sufficient or almost sufficient quantity in the diet. It is necessary to suppose that cod liver oil brings about maximal utilization of the minimal quantities of calcium or phosphorus in the diet. It greatly reduces waste of these elements and, therefore, must bring about maximal absorption from the alimentary tract. In human rickets, for example, the organism has lost its power to assimilate and to hold lime salts; if fed in large amounts, these salts are simply excreted. Cod liver oil (or radiant energy) furnishes something to the body which enables it to assimilate and hold lime salts. Obviously, cod liver oil makes the metabolic processes of the body, in respect to calcium and phosphorus, vastly more efficient. Its power to exert a regulatory influence on the calcium or phosphorus metabolism is perhaps to be regarded as an expression of an increased body efficiency.

What is the mode of operation of cod liver oil and by what means does it produce its extraordinary effects? On this problem of extreme interest no light can be shed at the present time. Certain it is that cod liver oil itself does not supply the deficient element. The existence of a latent period before the effect of cod liver oil becomes manifest makes it altogether likely that the effect of the oil is general and not limited to the alimentary tract. The almost exact similarity between the effects of cod liver oil and of radiant energy on the calcium and phosphorus metabolism of the body, and the existence of a similar latent period before the effects of radiant energy become manifest are additional strong evidence that the cod liver oil acts on the body as a whole rather than on the alimentary tract alone. Cod liver oil probably supplies something which is essential for optimal cellular function.

According to our conception, in the absence of the factor or factors contained in cod liver oil, and in the absence of radiant energy, the organism is laboring under a load, and the changes in the calcium and phosphorus metabolism resulting from the administration of cod liver oil are to be thought of as the result of the release from the load. The healing brought about by cod liver oil in rickets probably denotes in reality the manifestation of a restoration of normal function. Cod liver oil or radiant energy cannot be regarded in any sense as exerting a specific influence on calcium and phosphorus metabolism. The power to raise the calcium in the blood, when the calcium is low, or the phosphorus when that is low, is merely an isolated example of an effect which happens to be visible and measurable. Doubtless, cod liver oil and radiant energy will be found to have similar regulatory and efficiency producing effects in all conditions in which the organism is suffering as a result of a deficiency in the factor contained in cod liver oil or in radiant energy. When the human organism is deprived of the influence of radiant energy and of the factor or factors contained in cod liver oil, it loses its power to make successful adaptations to faulty environmental or dietetic conditions. What cod liver oil accomplishes in rickets is nothing more or less than the restoration to the organism of its power to make a successful adaptation to a faulty diet and a faulty environmental condition (roomlight). The evidence at hand does not indicate that cod liver oil or radiant energy causes the body to bring into action new or unusual processes, but rather that it restores to the organism power to utilize in the normal way and for the normal purpose those which were in operation all the time.

The similarity between the action of cod liver oil and that of radiant energy in rickets is so close that a connection must exist between them. So far as the calcium and phosphorus metabolism of the body are concerned, cod liver oil seems to be a substitute for radiant energy. It will be most interesting to see if, in the near future, a relation between cod liver oil and radiant energy will not be established of such nature that their effects will be explicable on a single basis.

THE HISTORY OF COD LIVER OIL AS A REMEDY *

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The revival of the use of cod liver oil in therapeutics and the newly awakened interest concerning its action have stimulated this inquiry into the history of its employment in medicine. The use of fish oils in medicine is mentioned by Hippocrates,[1] and Pliny [2] writes that the oil of the livers of the dolphin was used for chronic eruptions of the skin, not only as an external application, but also internally. No definite mention of the oil from the various species of *Gadus* is found in Greek and Roman literature (Bennett). Apparently, however, cod liver oil has been used by the fisherman along the coasts of northern Europe for many years. It is stated that, in the Island of Shetland and the north of Scotland generally, the liver of the cod has long been considered a special delicacy, and hence is given to invalids and people in poor health, particularly for "old pains," [3] and that the fresh oil from the livers was used as butter and considered especially delicious. The use of cod liver oil by physicians was first recorded in England by Darbey at the Manchester Infirmary in 1789, who wrote:

> A woman who laboured under the most excruciating rheumatism, and was an outpatient of this infirmary, being advised to rub her joints with the oil, was induced to take it at the same time internally. A few weeks restored her to the use of her limbs, and she was cured. However, little attention was paid to this case, as it was supposed that the alteration of the weather, and the medicine she had before taken, had caused the cure. About a twelvemonth afterwards, her complaints returned with double violence, and the same remedy restored her to health again. Encouraged by this second recovery, Dr. Kay (1766), one of the physicians to the infirmary, prescribed it for other patients, in similar cases; and it answered his most sanguine expectations. Since then, it has been used by the other physicians with the greatest success.[4]

The popularity of cod liver oil for chronic rheumatism became so great at the Manchester Infirmary that "near a hogshead annually" was used there. In 1771, Percival entered it in the British Pharmacopaeia; later, in 1790, he wrote thus of its effect in chronic rheumatism:

> While I was one of the physicians to this charity [Manchester infirmary], I had the fullest evidence of the successful exhibition of cod liver oil, in various maladies, of the class above described, which had resisted other power-

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* From the Department of Pediatrics, Yale University School of Medicine.

1. Fedotoff: De oleo Jecoris Aselli, Diss. Leipsic, 1842.

2. Pliny: Nat. Hist., Lib. **32,** p. 27.

3. Bennett: Treatise on the Oleo Jecoris Aselli, Edinburgh, 1848.

4. Percival's Essays, Ed. 4, 2:360, 1790.

> ful modes of treatment. And I frequently compared its operation with that of gum guaiacum, by prescribing each, at the same time, to different patients in similar circumstances. These trials almost always terminated in favour of the oil; and the patients, who took guaiacum, by conferring with their fellow-sufferers, were sometimes so sensible of making a slower progress toward recovery, as to request a change of one remedy for the other.

The observations of Dr. Bardsley[5] (1807) concerning its employment at the Manchester Infirmary also are interesting.

> From long and repeated experience, I am enabled to speak of it as a medicine of efficacious, but limited powers. In some instances, where every other means has proved unsuccessful, it has operated in a manner so decidedly beneficial, as to excite astonishment. But, on the other hand, it has frequently failed in some of the mild, and more common rheumatic affections. The circumstances under which I have found it most advantageous, when used both externally and internally, are the following: 1. In the chronic rheumatism of elderly persons, where the muscles and tendons have become rigid, and the joints nearly inflexible, in consequence of the disease having been brought on by excessive labour, hard fare, dampness, and cold. 2. In women whose constitutions have been worn out by repeated rheumatic attacks after parturition, and more especially in the decline of life. I have seen a few patients recover entirely by the exhibition of the oil; who, on their admission into the house, were unable either to preserve the body in an erect posture, or support its weight on the lower extremities.

It seems very probable that some of the cases of "rheumatism" in which the effects were "so beneficial as to excite astonishment" were osteomalacia.

Although undoubtedly cod liver oil continued to be a family remedy in different parts of the country, apparently it was little used by physicians during the next thirty years. At any rate, in the English medical literature of that period, no further mention of it has been found until its revival in 1841 by Bennett,[3] who had traveled in Germany and had observed its employment there.

In 1822, the Society of Science and Arts of Utrecht made the chemical and therapeutic properties of cod liver oil the subject of a prize essay.[6] Apparently, therefore, its use in scrofula and rickets was known to the Dutch medical profession at that time. Bennett states that, in Holland, it had obtained a wide reputation for the cure of rickets long before its remedial properties were acknowledged by medical men.

In the same year (1822), Schenck[7] published the first German article on cod liver oil as a therapeutic agent. This article deals with the details of a number of cases of rheumatism and gout which were greatly relieved or entirely cured by cod liver oil.

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[5] Quoted from Bennett (Footnote 3), p. 72.

[6] Hufeland's Journal **56**:128.

[7] Schenck: J. d. pract. Heilk. **55**:31, Part 6.

Schütte,[8] in 1824, published the first definite case histories of rickets cured by cod liver oil, stating that he had used it for twenty-five years. The cases he cited were in children, from 3 to 5 years of age, and unable to walk, who were cured in from five to nine weeks. In each instance, the parents or relatives had prescribed the remedy. He definitely attributed to Percival the introduction of cod liver oil into medical literature.

In 1826, Schenck[9] reported its successful use in four cases of rickets. He wrote:

> I am able to recall that my venerated teacher Michaelis in Marburg recounted to us in his lectures in special therapy, under the chapter on chronic rheumatism, that he had during his stay in England at the hospital in Manchester seen cod liver oil used with striking success against chronic rheumatism.

From this time on, numerous German authors wrote on the subject, and cod liver oil became very generally used throughout Germany for rheumatism, gout and rickets, and hence for scrofula and tuberculosis.

Even before the middle of the century accounts of failure and of contaminations and substitutes for real cod liver oil appeared in the literature. So great was the demand that all sorts of substitutes were used. In one instance, a substitute was even flavored with decayed herring to give the characteristic offensive taste and smell.

The introduction of cod liver oil into France, which came a few years later than in Germany, is described by Trousseau:[10]

> The manner in which M. Bretonneau, of Tours, was induced to give the oil in this disease deserves notice. He had treated the rachitic child of a rich Dutch merchant with preparations of iodine and other means, for some time, without success. He was then told by the father that the elder children had previously suffered under the same malady, and had been cured by the cod liver oil, which, in Holland, was a popular remedy. Bretonneau gave the same substance to his young patient, and was much struck with the very rapid and successful result which followed. He commenced making researches with it on other patients, and it was only then that he learnt for the first time what had been written by the German authors on this subject. He has since given it extensively in rachitis, with the happiest results. This fact was communicated to the Societe de Medecine de Paris, in 1837, by M. Roche.

In 1836, de Villards[11] published the first article in France on its therapeutic value, but it was not until Trousseau, about the middle of the century, taught of its use and related the experiences of his celebrated colleague Bretonneau that it became generally known and recommended.

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[8] Schütte: Arch. f. med. Erfahrung **79,** 1824.

[9] Schenck: Hufeland's Journal **62,** 1826; J. der pract. Heilk., 1826, Part 3, p. 2.

[10] Trousseau: Clinical Medicine, Philadelphia **2**:734, 1882.

[11] De Villards: Schmidt's Jahrb. **5**:147.

In each country, the experience was the same: Cod liver oil was used by the fishing people and peasantry; then accidentally observed by some physician, tried by him, and so made known generally to the profession. At first, it was used in chronic rheumatism and gout; then, naturally enough, in other bone and joint diseases, notably rickets and osteomalacia (which was considered closely allied to gout); then in scrofula, because of its supposed identity with rickets, and finally in other forms of tuberculosis. It is interesting that its use in tuberculosis should have been by the way of rickets and gout.

It is interesting, too, that despite the fact that it was so effective in rickets and despite the fact that this efficacy had been observed and carefully recorded by reputable and well-known medical writers, it should have fallen into such widespread disuse. It is well recommended and reported as late as the middle of the nineteenth century; but late in that century and early in this one the textbooks of pharmacology all speak of cod liver oil as being useful in tuberculosis and rickets because, and only because, it is an easily digested and easily assimilated fat (Potter, 1902; Stevens, 1903; Penzoldt, 1904; Hare, 1907; Cushny, 1911 and 1915; Sollmann, 1917). At the same time appear numerous notes as to the detection, in samples then on the market, of adulteration or substitution of other oils, and also clinical reports both of success and of failure in its therapeutic use. Heubner, Salge, Baginsky, Biedert and Fischl found it of no use in rickets. Vierordt, Stöltzner and Finkelstein maintained a vigorous defense of it, although they emphasized the importance of combining it with phosphorus. From 1908 to 1912, Schabad published the much-discussed metabolism experiments, which indicated a specific effect in rickets not produced by other oils. He pointed out certain pitfalls in relation to latent period and dosage. In 1910, Rosenstern[12] wrote: "Cod liver oil is in the forefront of children's remedies. For long it has been struggling against the scepticism of exact science." He reported cures in cases of early rickets and tetany with cod liver oil alone, and considered the effect specific. Czerny,[13] in 1912, asserted most positviely that its only effect was due to its easily assimilated fat. No definite reports of its failure in actual use appeared in the literature in this country or in England. However, pharmacologists and chemists were convinced that its action was in no way specific, and certain noted pediatricians, whose influence was widespread, taught that it was of no particular value. In the 1901 edition of Rotch's[14] "Pediatrics," he says:

> The treatment of rachitis is essentially dietetic and hygienic. The infants should be kept in the open air as much as possible, and should live in rooms

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[12] Rosenstern: Berl. klin. Wchnschr. **47**:822, 1910.

[13] Czerny: Therap. d. Gegenw. **80**:49, 1912.

[14] Rotch, T. M.: Pediatrics, Philadelphia and London, 1901, p. 341.

> accessible to sunlight. There does not seem to be any drug which produces specific effect upon the osseous changes which take place in rachitis. Phosphorus is considered by some observers to be a valuable adjunct in the general dietetic and hygienic treatment, but, according to our experience at the Children's Hospital, it has not proved to be of any special benefit.

He makes no mention of cod liver oil.

Still,[15] in his textbook, in 1912, notes the use of cod liver oil and gives the dosage, and adds:

> There seems to be no specific virtue in cod liver oil, .any other oil will do equally well, provided it can be taken without disturbing digestion or causing nausea by its taste. At one time we used, at the Children's Hospital, Great Ormond Street, olive oil and pilchard oil and cotton seed oil, made into as palatable an emulsion as possible, and these seemed to be as useful as cod liver oil, except that they were more apt to cause nausea or digestive disturbance.

Henoch, 1882;[16] Meiggs and Pepper, 1886;[17] Starr, 1894;[18] Holt, 1896;[19] Kerley, 1907,[20] and Fischer, 1907,[21] in their general textbooks, advised the use of cod liver oil, and many physicians were impressed with its obvious benefit in rickets and continued its use. Recently, well controlled experiments both in the rat and in the human infant have demonstrated beyond criticism the efficacy of cod liver oil in the cure and prevention of rickets, and attention may now be directed to the mechanism which brings about this effect.

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[15] Still, G. F.: Common Diseases of Childhood, London, 1912, p. 103.

[16] Henoch: Lectures on Diseases of Children, London, 1882, p. 335.

[17] Meiggs and Pepper: Practical Treatise on Diseases of Children, Philadelphia, 1880, p. 705.

[18] Starr: American Textbook of Diseases of Children, New York, 1894.

[19] Holt, L. E.: Diseases of Infancy and Childhood, New York, 1896.

[20] Kerley: Treatment of Diseases of Childhood, New York, 1907, p. 443.

[21] Fischer: Diseases of Infancy and Childhood, Philadelphia, 1907, p. 353.

THE ANATOMIC BASIS FOR INTERPRETING ROENTGENOGRAMS IN RICKETS *

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For many years, clinicians have been familiar with certain of the features which characterize the roentgenograms of rachitic human bones; but a careful analysis of them has not been made, nor has the interpretation of the picture in the light of histologic alterations received any great attention. This investigation, which was begun at the suggestion of Dr. E. A. Park and carried on largely through his continued interest, was undertaken with a view to ascertaining the anatomic basis for the roentgen-ray changes in the skeleton in rickets.

METHOD

The bones selected for study were cleaned of surrounding tissues and cut into slices from one-eighth to one-quarter inch thick through the epiphyseodiaphyseal junction. Roentgenograms were obtained, and the slices were then used for the preparation of histologic sections. Some of the tissues were partially decalcified in Müller's fluid; but in many instances, it was found possible to cut sections without preliminary decalcification. The celloidin technic was used throughout. The sections were stained either with hematoxylin and eosin, by Mallory's method, or with hematoxylin and silver nitrate, as suggested by Von Kossa.

In studying the material obtained from thirty-five cases, comparisons were made between the histologic sections and the roentgenograms in order to ascertain the elements in the former responsible for the characteristic shadows of the latter. It was hoped that by this method some new facts would be found which would make possible an earlier clinical diagnosis.

ROENTGENOGRAMS IN RICKETS

The roentgenographic changes which occur in the bones of the extremities in the course of rickets will be considered first. The discussion will be limited to alterations of a more or less fundamental nature. One of the most constant findings when the roentgenogram of a bone during the active stage of rickets is examined is the general rarefaction. This varies in degree but is undoubtedly present to a cer-

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tain extent in every case, although it will be overlooked when of a mild degree on account of the lack of any standard for comparison. In other cases, the general osteoporosis may be most conspicuous, and the shafts of the bones may appear as nearly transparent shells, not much more dense than the surrounding tissues.

Little change is to be noted in the cartilage at the ends of the bones. In normal as in rachitic bone, the outline of the epiphyseal cartilage is generally invisible because its density is the same as that of the surrounding softer tissues. But, because of changes which make the shaft appear shorter, the cartilage will necessarily seem longer, or the distance between the shaft and epiphyseal center will seem greater; although, on close observation, it is at times apparent that, in the region where the added length seems to be, that is, between the true cartilage and the visible shaft, the density is slightly less than in the cartilage itself. The signficance of this area will be referred to later.

Probably the most definite signs are to be found at the ends of the shafts of the bones where they unite with their cartilages, more particularly in those locations where growth is proportionately rapid, the costochondral junctions of the middle ribs; the upper ends of the tibia and humerus, and the lower ends of the femur and radius. Clinically, we are all familiar with the enlarged epiphyses of rickets, and the rachitic rosary formed at the costochondral junctions. This enlargement is evident in roentgenograms. On account of accompanying rarefaction, its full extent often will not become visible until healing is moderately well advanced.

The changes at the ends of the shafts are more characteristic. In roentgenograms of normal bones, the line of termination of the shaft is quite sharp. It appears either as a single line of slightly greater intensity than the rest of the shaft; or, more frequently, in a sharply focused plate, the line will be double, this double line being the boundary of the surface in which the shaft terminates. In the rachitic bone, the sharp termination disappears, and the shaft fades away into the cartilage by a succession of less and less intense shadows. The transition may be very gradual, so that the shaft seems to be capped with a fringe an inch or more in width; or it may occur quickly, and at times abruptly. Sometimes, it may be observed that, at the base of this fringe, the shaft is crossed by a definite line of increased density, suggesting the termination of a normal shaft with a fringe sprouting from it. With the onset of healing, a definite line, at times seeming double because it is the boundary of a surface, appears on the epiphyseal side of this fringe, and will thus be separated from the shaft by a distinct hiatus. As healing progresses, the line thickens, and the hiatus gradually disappears.

Another alteration is frequently observed. The shaft is longer at its periphery than in the middle. In mild cases, there is only a small lip of bone at the edges, extending just beyond the line of termination of the middle portion of the shaft; in a more advanced state, the whole end of the bone appears concave. By the use of stereoscopic plates, it can be demonstrated that the actual deformity consists in a hollowing out or a cuplike depression of the ends of the bones. The cupping is much more striking when the termination of the shaft has been sharply outlined by the healing process.

In many cases, the cortex of the bone presents no characteristic changes. In others, especially when the disease has been of long duration, it is frequently observed that the cortical lamellae have lost their compact structure, and have become arranged in a much more loosely woven pattern. This appearance of lamination has not been generally appreciated, but seems to be as characteristic of rickets as any other.

Although, as a rule, the periosteum, in rachitic as in normal bone, is not visible, at times it may appear raised from the cortex and markedly thickened, resembling closely the roentgenogram in a syphilitic periostitis. It may not be possible to differentiate the two. It is to be observed, however, that the periosteal trabeculae produced by a rachitic hyperplasia at times tend to assume a stepladder appearance; that is, to lie at right angles to the long axis of the bone. A distinct hiatus is invariably observed, separating the periosteum from the cortex. The thickened periosteum is more frequently found on the concave side of the long axis of the bone than on the convex side. No such predilection is shown by syphilis.

The thickened periosteum is more commonly seen in the picture of rickets in its healing phase. A child who has active rickets may give no roentgenographic evidence that the periosteum is involved, and yet, a few weeks later, when healing is in progress, the plates will show plainly the effect of marked periosteal hyperplasia, so pronounced that it must have been present when the first picture was taken.

The changes observed in the epiphyseal centers of ossification, while similar to those in the shaft, are of particular interest. The degree of rarefaction is often pronounced; indeed, it may be so marked that the entire nucleus is rendered invisible or appears as a punched out hole in the center of the epiphyseal cartilage. In other cases, when the disease had set in before the time of the appearance of the nucleus of ossification, it may never have been visible by means of the roentgen ray. Epiphyseal centers which are visible during the active stage of the disease lose their normal sharp outline and, like the ends of the shaft, fade gradually into the cartilage. After the beginning of antirachitic therapy and the establishment of healing, a previously invisible nucleus may become quite distinct. Other nuclei will immediately lose their indefinite outline by being surrounded by a clearly defined ring, making the nucleus appear at once larger, and doubly contoured. As healing progresses, the double border gradually grows together.

Evidence that a bone at some previous time showed signs of rickets may not be absent from the roentgenograms even when the disease has been healed for a long time and when the normal growth of the bone has carried the epiphyseal line considerably beyond the old site of the process. In these cases, a dense line may be seen crossing the shaft transversely at some distance from the growing end, this line marking the termination of the shaft at a time when the rickets was active, and having been formed by lime salts deposited at the onset of healing. In cases in which the disease has shown several periods of activity with intermediate healing, the shaft may be traversed by more than one of these lines. Now and again, when alternate periods of activity and healing have occurred with frequency and rapidity, the whole end of the bone may present a mottled, honeycombed appearance, due to the overlapping in different planes of the several epiphyseal lines.

PATHOLOGY OF RICKETS

In normal bone, the largest part of the epiphysis consists of a mass of undifferentiated cartilage cells. As the diaphysis is approached, the cells begin to swell and take on a more rounded form, and to be arranged in columns. The infiltration, with lime salts, of the intercellular matrix among the lower cells of these columns produces the epiphyseal line. The calcified intercellular substance serves to direct the marrow blood vessels against the rows of cartilage cells, and they are destroyed in an orderly fashion as the growth of the bone goes on. The calcified matrix is itself destroyed by osteoclasts and replaced by trabeculae through the activity of osteoblasts. The new bone is first laid down as osteoid tissue, which differs from mature bone only in a lack of lime salt deposits, but, in health, calcification is rapid, and only a narrow rim of osteoid is ever found. Growth in thickness is much slower and is carried on by subperiosteal osteoblasts. In the marrow cavity, the trabeculae are few in number and very loosely interwoven; while, in the cortex, they are numerous and thick, giving to it a dense and homogeneous appearance. It is important to keep in mind that the trabeculae are being continuously resorbed by osteoclasts and replaced in modified form by osteoblasts, so that the adult bone will finally be evolved in its permanent form.

In rickets, the primary fault lies with the process of calcification. The cartilage continues to grow at a normal rate; but owing to the absence or irregularity of calcium deposition, the orderly destruction of the cartilage by the marrow elements and the conversion of the calcified intercellular substance into the shaft are interfered with. Diaphyseal elements, consisting of blood vessels and surrounding osteoid and connective tissue, are found invading the epiphysis in a more or less lawless fashion. The ultimate result is a wide area between the true epiphysis and diaphysis corresponding to the destroyed epiphyseal line and consisting of scattered areas of osteoid tissue, connective tissue, blood vessels and cartilage cells. This area has been termed the metaphysis. It is deficient and at times entirely lacking in lime salt deposits. In the shaft, the processes of resorption and deposition continue to go on as normally, but with this difference: the newly formed bone does not become ossified, but remains in the form of osteoid tissue, which thus comes to form a rim about the old trabeculae. The peri-

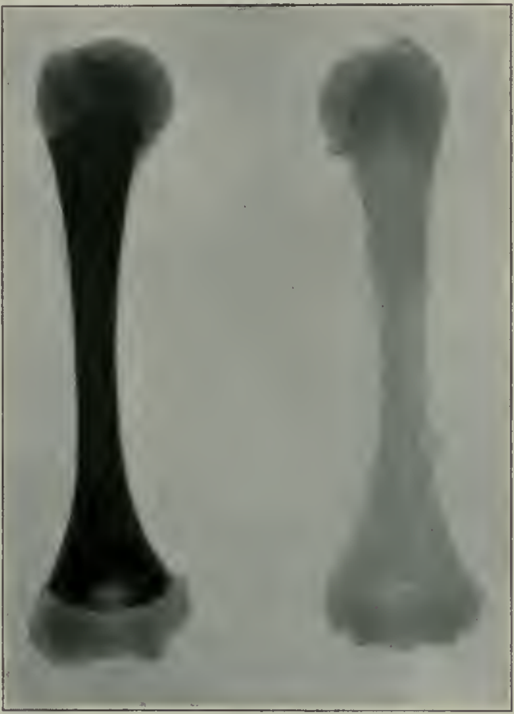

Fig. 1.—The left humerus of a full term infant after decalcification in nitric acid compared with the corresponding normal bone from the right side. The removal of the lime salts has destroyed the characteristic features of the bone, and the formerly dense shaft is even more permeable to the roentgen rays than the cartilage.

osteum as a rule is not altered, but occasionally there are signs of an active hyperplasia, with considerable thickening.

When healing begins, as Schmorl has shown, there first occurs a deposition of lime salts between the cartilage cells on the epiphyseal side of the metaphysis, where calcification normally occurs and presumably would have occurred had there been no rickets. As time goes on, the new line is broadened; the osteoid tissue in the metaphysis and in the shaft is ossified, and normality is regained. If at any time there is a recurrence of the disease, the new epiphyseal line will be broken through in numerous places by the again invasive marrow elements, and the line of calcification corresponding to the period of healing will be buried in the widening metaphysis. Occasionally, two, three or even more of these buried lines of calcification may be found, indicative of so many frustrated attempts at healing.

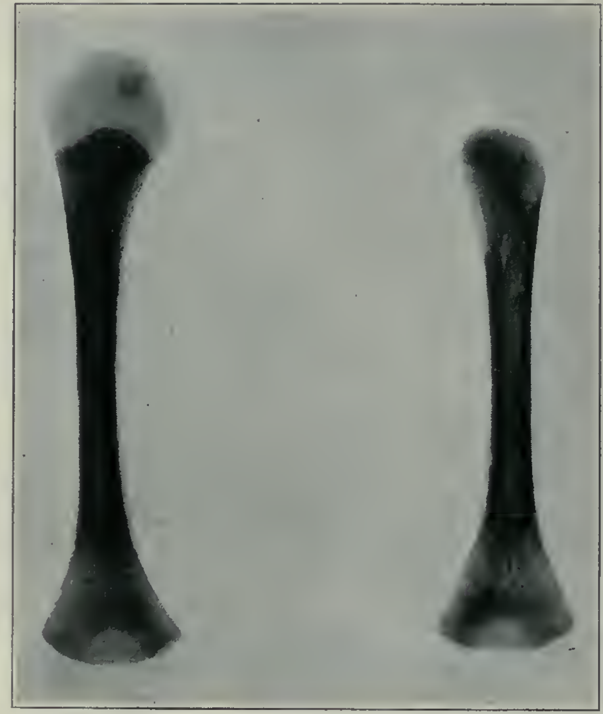

Fig. 2.—The two humeri of a full term infant: the one on the left normal, the one on the right after the removal of its organic and constituents with alkali. Except for the disappearance of the cartilaginous ends, and the slightly greater distinctness with which the individual lamellae have been outlined, there is strikingly little change.

ANALYSIS OF SHADOW CASTING ELEMENTS

The foregoing description of the histologic findings will serve to point out the elements which go to make up normal and rachitic bones. An attempt has been made to determine which of these are responsible for the shadows in roentgenograms. In general, every tissue offers some obstruction to the passage of the rays; but since in life the bones are always surrounded by muscles, skin, etc., we are necessarily interested mainly in those elements which cast a shadow of greater or less intensity than the surrounding soft tissues, as only these will be distinguishable when analysis is attempted. It has already been mentioned that the cartilage of the epiphysis is generally invisible. Nor is it possible by roentgenograms to distinguish between undifferentiated cartilage and the proliferative zone, although in histologic sections the difference is marked. They are equally permeable to rays.

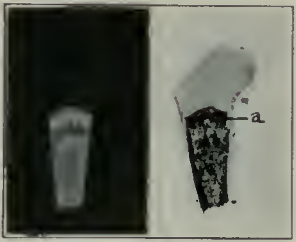

Fig. 3.—A section through the end of a bone, with marked syphilitic osteochondritis, stained with nitrate of silver, contrasted with the roentgenogram of the slice of bone from which the section was cut. The broad band of calcified intercellular substance (*a*) has cast an especially intense shadow.

It is quite generally stated that the greater density of the shaft is due to the presence of lime salts, as clinical experience teaches that lime salts wherever deposited will obstruct the roentgen ray. The calcified tuberculous kidney and the calcified plaques of arteriosclerotic vessels are familiar examples. To verify this, both humeri were removed from an infant with a normal skeleton. One of these was preserved in neutral formaldehyd,[1] the other was completely deprived of inorganic salts by the action of 5 per cent. nitric acid. Roentgenograms were then taken on one plate of the two side by side. Microscopic sections cut from the decalcified humerus showed that the histologic structure had not been changed by the action of the acid. The roentgenogram demonstrated beautifully that the increased density of the shaft is due entirely to the presence of inorganic salts. Indeed, the decalcified diaphysis seemed somewhat more permeable to the roentgen rays than the overlying epiphyseal cartilage.

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[1] We have determined by pictures made before and after treatment with neutral formaldehyd that the fixing process does not alter the roentgen-ray picture.

The converse of this experiment was next attempted, to determine the part played by the organic component. For this purpose, two infantile humeri were again selected, one of them being preserved as before. The other was deprived of organic substances by a thorough boiling in a 5 per cent. solution of potassium hydroxid. After washing, the specimens were roentgenographed, and the second then placed in dilute acid, where, except for a slight cloud, it rapidly and entirely dissolved, showing that the removal of organic matter had been fairly complete. The alkali treatment had, of course, removed the epiphyseal cartilages, but, except for this, the roentgenographic pictures of the two bones were strikingly similar. On close examination only could it be made out that the trabeculae of bone were slightly more sharply defined after removal of the organic component.

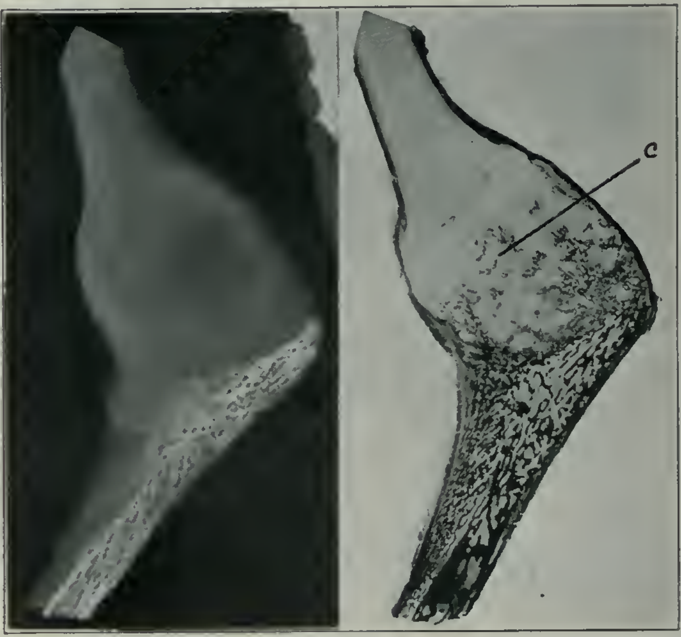

Fig. 4.—Section through a costochondral junction in a case of florid rickets stained by Mallory's connective tissue method and the roentgenogram of the slice of bone from which the section was cut. The abundant growth of connective tissue (*c*) in the metaphysis has not produced a corresponding shadow in the roentgenogram.

These two experiments serve to emphasize the importance of calcified tissues from a roentgen-ray standpoint. Of these tissues, there are two types: (1) calcified intercellular matrix and (2) calcified trabeculae. Both cast sharp shadows, but the shadow due to the former is especially intense. This is shown by the sharp line in which normal bone terminates, and by the new line which is formed when rickets begins to heal, but is much more vividly illustrated by the broad intense band which occurs in early hereditary syphilis. Careful comparisons of these more intense areas with the corresponding histologic sections will show that in each instance they are due to calcified intercellular substance. By cutting sections without decalcification and having them pictured by the roentgen ray, it has been shown that osseous trabeculae one-fifth millimeter in thickness cast a definite shadow and that trabeculae of one-half this thickness are often readily distinguishable.

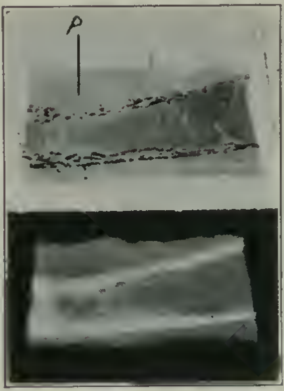

Fig. 5.—Section stained with hematoxylin, eosin and silver nitrate contrasted with a roentgenogram of the slice of bone from which the section was cut. Hyperplasia of the periosteum (*p*) has occurred on both borders of the shaft; the so-called rachitic periostitis. The thickened periosteum, composed almost entirely of osteoid tissue, does not cast a shadow with the roentgen rays.

It was next thought advisable to ascertain to what extent blood might influence the passage of roentgen rays. The rachitic metaphysis is considerably more vascular than any area in normal bone, and it was conceived that this might be a significant factor. An experiment was performed on a dog 5 months old, which was anesthetized with ether, the blood vessels to both hind legs being exposed by a midline abdominal incision. The right hind leg was congested with blood by injecting 5 c.c. of a 1 per cent. solution of sodium nitrite to dilate the capillary bed, and then ligating the common iliac vein on that side. When the congestion seemed complete, the artery also was ligated and the dog killed. The blood was completely washed from the left hind leg by allowing 3 liters of salt solution to run in the arterial and out the venous side of the circulation. The whole lower half of the dog was then placed in formaldehyd for fixation, and later removed and the various bones from the two sides roentgenographed side by side. No essential difference in the pictures could be made out, showing that blood does not materially alter the permeability of bone to the roentgen ray.

Because of the nature of the rachitic process in which an excess of connective tissue is formed in the metaphysis, it has been possible to determine that this tissue does not noticeably affect the roentgen-ray picture. In one case, which is illustrated, a section through the costochondral junction, stained with Mallory's connective tissue stain, showed a luxuriant growth of connective tissue in the metaphyseal zone, yet the roentgenogram of the slice of bone from which the section was cut gave no indication of this growth.

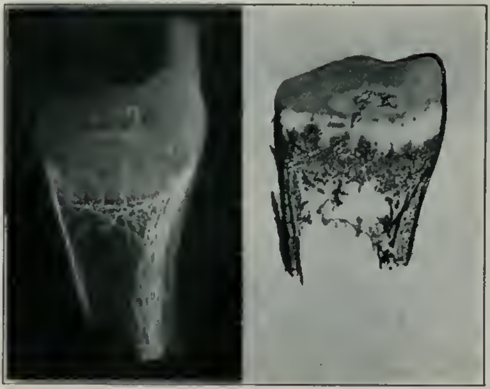

Fig. 6.—Section of rachitic bone from the lower end of the tibia stained with Mallory's connective tissue stain, and the corresponding roentgenogram. In this case, the "fringe" produced by the invasion of the cartilage with marrow elements corresponds in extensiveness with the similar "fringe" in the roentgenogram. On microscopic examination, small bits of osseous tissue are found throughout the metaphysis.

Likewise, osteoid tissue, which histologically is similar to other connective tissues, only more compact, seems to be a negligible factor from a roentgen-ray standpoint. In one marked case of rickets in which there had been considerable periosteal hyperplasia unaccompanied by any calcification, the thickened periosteum, composed almost entirely of osteoid tissue, was quite invisible in the roentgenogram. In other cases, not at all infrequent, scattered areas of osteoid tissue throughout the metaphysis have failed to show in the roentgenogram.

The rachitic metaphysis requires special consideration. Anatomically, it is a composite of cartilage, connective tissue, blood vessels containing blood, osteoid tissue and a variable amount of osseous tissue. This last tends to be more abundant toward the diaphyseal border of the metaphysis. We are already familiar with the type of shadow the calcified tissue will cast, and this type will come into dominance as the diaphyses approach. But the epiphyseal border of the metaphysis is usually free from lime deposits. This border zone is somewhat more permeable to the roentgen rays than the adjacent cartilage and is often seen as a dark band between the indistinct termination of the shaft and the epiphysis. At first glance, one obtains the impression that the dark band is due to the proliferative zone of cartilage at the lower border of the epiphysis, but careful comparisons of sections with roentgenograms show conclusively that this is not the case. In many cases, this dark band may be indistinct or absent, seemingly owing either to imperfect roentgenograms or to varying permeability of this portion of the metaphysis. It was never so conspicuous in plates taken during life as it often was in the roentgenograms of slices of bone obtained after death.

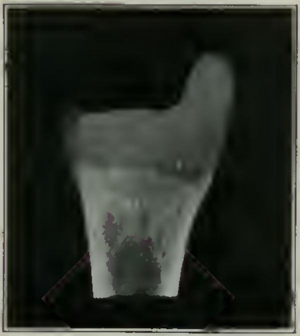

Fig. 7.—A slice of bone in which the full extent of the metaphysis is not indicated by the length of the "rachitic fringe." The dark transverse band, seen between the end of the shaft and the cartilage, is due to a portion of the metaphysis which is entirely free from osseous tissue.

The shadow cast by the marrow cavity is largely characterized by the interlacing osseus trabeculae which traverse it. When all lime salts are removed, as was shown by the acid-decalcification experiment, it is slightly more permeable than normal cartilage. The cortex owes its density to high concentration of calcium deposits. The periosteum is not visible. Even a thickened hyperplastic periosteum will not show unless the hyperplasia is accompanied by some calcification.

INTERPRETATION OF ROENTGENOGRAMS

We are now in a position to understand the meaning of the changes in the roentgenograms produced by rickets. The general rarefaction is due to the disturbance in calcification. Normal bone is composed, roughly, of two parts inorganic matter to one part organic matter. In rickets, the proportions are reversed. But the osteoporosis associated with rickets differs in one important respect from that seen in most other diseases. In scurvy, in osteogenesis imperfecta, in the atrophy following nonuse and in the osteoporosis of old age, there is an actual atrophy of the lamellae. In rickets, the lamellae remain normal in size but are composed largely of osteoid tissue, and the central portion only is calcified. With healing, the density slowly returns to normal through gradual calcification of the osteoid rim. This begins centrally about the remaining osseous deposits and moves toward the periphery.

The epiphyseal cartilage, when the outline is visible, appears longer than in normal bone because it seems to embrace the upper portion of the metaphysis. When healing occurs, the initial deposit of lime salts in the lower border of the proliferative zone of cartilage marks sharply the boundary of the epiphyseal cartilage, and it at once appears shorter, though in reality there has been no change.

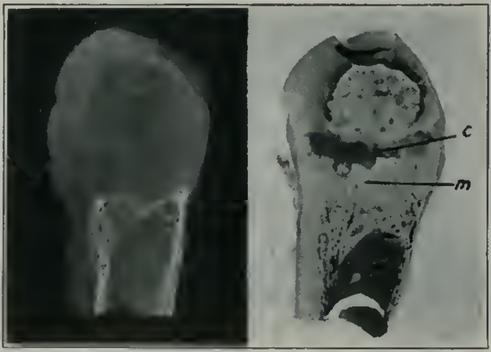

Fig. 8.—Roentgenogram and histologic section stained with hematoxylin and silver nitrate taken from the lower end of the femur of a rachitic colored child, 1 year old. The zone of proliferative cartilage (*c*) shows distinctly in the section as an irregular dark band and marks out the distal boundary of the metaphysis. The broad metaphyseal zone (*m*) has produced no corresponding shadow ("fringe") in the roentgenogram.

The fringe-like termination whereby the shaft gradually merges with the cartilage is the most characteristic feature of the roentgen-ray pictures. The marrow vessels which spring from the shaft to invade the cartilage, carrying with them surrounding areas of connective tissue, osteoid and fragments of osseous tissue, may be likened to so much luxuriant foliage sprouting from the end of the shaft of the bone. The connective tissue, corresponding to the leaves, does not leave a record on the plate, but the calcium deposits in the stems do. Therefore, the roentgenograms do not give a complete idea of the extent of the invasion. This is well shown in sections stained by Mallory's method. When compared with roentgenograms, it can be seen that the fringe is more extensive in the former and reaches further toward the epiphysis. The extent to which the fringe-like termination in sections stained by Mallory's method will coincide with the similar appearing termination in roentgenograms depends largely on the presence of scattered lime salt deposits. In some cases, a most luxuriant growth of connective tissue will have absolutely no corresponding shadow in the roentgenogram. These we are inclined to regard as cases in which calcification ceased entirely after the onset of the disease. In other cases, there may be almost complete coincidence between the two fringes; and here we may consider the course of the disease as mild, with calcification never ceasing entirely and the duration roughly proportional to the length of the fringe. But in the usual case which we have described, the connective tissue fringe of histologic sections extends farther toward the epiphysis than the corresponding termination of the roentgenograms. This may be taken to indicate an insidious onset of the disease, with gradual but finally complete cessation of calcification.

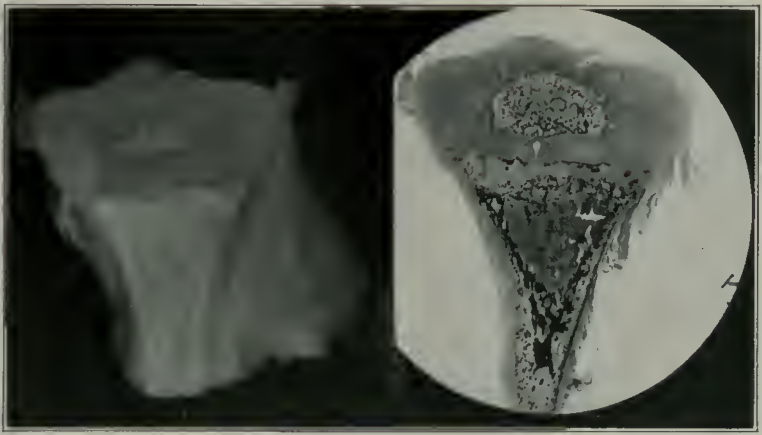

Fig. 9.—Roentgenogram and histologic section (stained with silver nitrate and hematoxylin) of a slice of bone taken from the upper end of the tibia in a rachitic child of 11 months, who had received treatment with cod liver oil for a period of one month. The section shows the new line of lime salts in the lower border of the epiphyseal cartilage and the lime-free hiatus which results at the end of the shaft. The roentgenogram shows shadows corresponding to the areas of calcification.

In healing, the initial line of deposit in the proliferative cartilage lies just beyond the top of the connective tissue fringe. In roentgenograms, therefore, its onset is attended by a seeming increase in length, and a hiatus is left between the new line and the shaft termination, which is gradually filled in as ossification brings about a slow return to normal.

Not infrequently, the roentgenograms will show a transverse line crossing the bone just below the beginning of the fringelike ending. This is due to the arrangement of the lamellae in that region, and probably marks the original end of the shaft before the onset of the disease.

The explanation of the cupped-out depression so frequently seen at the end of the shaft is forthcoming when we consider the firm elastic condition of the cartilage and the softened state of the rachitic bones. Because the bones are constantly pulled together by normal muscle tone and muscular activity, the end of the shaft mushrooms, spreading out along the lines of least resistance. The concavity is ordinarily distinct enough during the active phase of the disease, but is poorly outlined because of the indistinct termination of the shaft. In the phase of recovery, the new calcium deposits accentuate this appearance. The increased size of the epiphyses and the enlarged costochondral junctions are due partly to this mushrooming and partly to a thickening brought about by nature to meet the new functional demands, in accordance with the principle of Wolff's law. The bones are most deficient in lime salts at their growing ends and are therefore weakest at that place. Thickening takes place in order to bring added strength.

We have mentioned the distinctive laminated appearance of the cortex which may develop in the course of the disease and which shows plainly in the roentgenograms. This, too, may best be explained by the principles involved in Wolff's law. The new arrangement of the lamellae in the cortex of the bone, whereby the same amount of osseous tissue is spread over a greater area by means of a more loosely interwoven pattern, gives greater strength to the bone.

Now and again, a periosteal hyperplasia occurs in rickets, but the thickened periosteum does not cast a roentgen-ray shadow unless some calcification has taken place; that is, osteoid tissue formed by the periosteum is of the same density as the neighboring muscles. This explains why the administration of cod liver oil and the resulting return of calcification may be followed by the sudden appearance of a previously invisible periosteum.

The explanation for the changes in the epiphyseal centers of ossification are analogous to those for the alterations in the shaft. Invisibility or the degree of faintness depends on the amount of calcification. Growth occurs along the circumference of the nucleus, and the indistinct boundary here is exactly similar to that seen at the end of the shaft. The roentgen-ray picture of the nucleus is smaller than the real nucleus because the peripheral sprouts of connective tissue do not cast a shadow. With the onset of healing, intercartilaginous calcium deposits immediately surround the nucleus, giving the double-contoured effect, so that in the roentgenogram it at once looks larger.

One more feature of the roentgenogram in the healing phase deserves special explanation. It has been noted that the new line which appears as the result of the resumption of calcification in the cartilage will frequently appear to be double, or in the form of an ellipse. The double line is really the boundary of the surface of the new plane of ossification. Why the boundary of the plane should cast a more intense shadow than the central portion is made clear by a study of the histologic sections, in which it may be seen that the new epiphyseal line is broader and more completely calcified at the periphery than in the central portion.

SUMMARY AND CONCLUSIONS

The only element which constantly casts a shadow in roentgenography of rachitic bones seems to be calcium, in the form in which it normally appears in bone. Those tissues which, normally calcified, have become decalcified either leave no record or do so only by casting a negative shadow. These simple facts, combined with an understanding of the pathology of rickets and its variations, enable us not only to explain the shadows which characterize rickets roentgenographically, but also to predict with a fair degree of accuracy, from the examination of a roentgenogram, the actual histologic alterations.

SICKLE CELL ANEMIA

REPORT OF TWO CASES IN CHILDREN, WITH NECROPSY IN ONE CASE

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J. B. Herrick,[1] in 1910, reported a peculiar dyscrasia characterized by severe anemia, with the occurrence in the blood of elongated and sickle-shaped erythrocytes. Three instances of this condition have since been described, one by R. E. Washburn;[2] one by Cook and Myer,[3] and one by V. R. Mason.[4] Emmel[5] further studied the blood of Cook and Myer's case, demonstrating the existence of phagocytosis of the erythrocytes by large mononuclear leukocytes in the peripheral circulation. He also pointed out the fact that when sealed sterile preparations of the fresh blood were allowed to stand at room temperature for varying periods of time, many of the circular erythrocytes underwent transformation into elongated and sickle shapes similar to those seen in the freshly drawn blood. Furthermore, he showed that the blood of the patient's father, though normal to all appearances when drawn, underwent similar changes on standing. Guthrie and Huck[6] refer to a fifth case of sickle cell anemia, as yet unreported. Dresbach[7] and Bishop[8] have called attention to the occurrence of elliptic cells in human blood in patients with no other evidence of abnormality. The blood picture in their cases was, however, quite different from that in the others referred to.

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* From the department of internal medicine, University of Georgia Medical Department.

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[3] Cook, J. E., and Myer, J.: Severe Anemia with Remarkable Elongated and Sickle-Shaped Red Blood Cells and Chronic Leg Ulcers, Arch. Int. Med. **16**:644 (Oct.) 1915.

[4] Mason, V. R.: Sickle Cell Anemia, J. A. M. A. **69**:1318 (Oct. 14) 1922.

[5] Emmel, V. E.: A Study of the Erythrocytes in a Case of Severe Anemia with Elongated and Sickle-Shaped Red Blood Corpuscles, Arch. Int. Med. **20**:586 (Oct.) 1917.

[6] Guthrie, C. G., and Huck, J.: On the Existence of More than Four Iso-Agglutinin Groups in Human Blood, Bull. Johns Hopkins Hosp. **34**:43 (Feb.) 1923.

[7] Dresbach, M., quoted by Bishop, F. W.: Elliptical Human Erythrocytes, Arch. Int. Med. **14**:388 (Sept.) 1914.

[8] Bishop, F. W.: Footnote 7.

A study of the blood pictures and clinical findings in the reported cases and in our two cases leads us to the belief that sickle cell anemia is probably a definite clinical entity. Also we are quite convinced that the condition is familial. An analysis of the symptoms and signs common to the reported cases (Table I) gives the following information. All cases have occurred in negroes or mulattoes, with no special selection for sex. Evidences of severe anemia existed in every case. A definite and characteristic blood picture was present in all cases. Scleral discoloration, recorded as "a greenish tinge" or "tinge of yellow" was constant. Splenic enlargement was absent in all cases except our Case 2. (This patient had a severe malarial infection seven months before admission to the hospital.) Leg ulcers, which were present in all four reported cases, were absent in our two cases. Severe recurrent abdominal pain was mentioned by every patient except Cook and Myer's. General glandular enlargement, arthritic pain with occasional swelling of joints, edema of feet and ankles, cardiac enlargement and urinary abnormalities were not all present in every case, and these symptoms are so frequently present in cases of prolonged secondary anemia that we feel they are to be interpreted as manifestations of the anemia present in the cases under discussion rather than symptoms of sickle cell anemia.

As regards evidence pointing to a congenital or familial pathogenesis in this condition, the following points may be noted. Presumptive evidence of anemia, namely, general weakness, indisposition to exertion and dyspnea, dated back to childhood in the cases of Herrick, and Cook and Myer. In Washburn's and Mason's cases, they dated from the patients' earliest recollection. In our Case 1, weakness began at the age of 2 years. In the cases of Herrick and Mason, no family history of significance could be elicited. In Washburn's case, the family history carried a high child mortality, four sisters and four brothers having died in infancy and childhood from undetermined causes except in the case of one sister who died of "brain trouble." Cook and Meyer gave special attention to the family history, stating that all the children, two brothers and two sisters, had suffered from severe anemia. The case of one of the girls was reported. The sister died at the age of 22, of tuberculosis. It was stated that, at the age of 5, she had grown thin and sallow and had had pains in the extremities. Both the brothers died of anemia. Dr. E. W. Sanders saw the children and made the following notation: "I found the children the victims of a severe anemia. One of them died, and I then lost sight of the family."

In the four reported cases, the blood of relatives of the patient was examined in only one instance. The blood of the father in Cook and Myer's case was normal on being drawn, but "sickled" after standing

TABLE 1.—*Summary of Chief Points of Interest in Cases of Sickle Cell Anemia*

	Herrick's Case	Washburn's Case	Cook and Myer's Case	Mason's Case	Case 1	Case 2
Race........................	Negro	Negro	Mulatto	Negro	Negro	Negro
Sex........................	Male	Female	Female	Male	Male	Male
Age........................	20 years	25 years	21 years	21 years	5 years, 7 months	6 years
Presumably onset of symptoms referable to anemia	At age of 10 years, following attack of yaws	"Weak all her life"	Ulcer of leg at age of 5 years	Patient was weak and sickly as far back as he could remember	At 3 years of age	At age of 6 (present illness)
Family history............	Father died of accident; mother and three brothers healthy	Father in bad health for many years; mother died of "rheumatism"; four sisters and four brothers died in childhood; causes of death unknown except "one sister died of brain trouble"	Father living, condition of health not mentioned; mother died of cancer; two brothers said to be the victims of severe anemia of which one died at age of 7, the other at age of 17; one sister, who died at 22 of tuberculosis, began to grow thin and sallow at age of 5 and suffered with pains in the extremities	Fragmentary; no evidence of others in family being affected	Paternal grandfather living and well; paternal uncle living and well; maternal grandparents, no information; mother living and well; three brothers, two apparently healthy, one weak, dyspneic, suffers from abdominal pains and articular pains; one sister died at age of 5 days from hemorrhagic disease of newborn; one sister 10 months old, living and well	No information as to grandparents; father and mother living and well; nine siblings all living and well
Leg ulcer....................	At age of 10	At age of 20	At age of 5	At age of 21	No ulcer	No ulcer
General glandular enlargement	Present	Present except axillary glands	Not mentioned	Present	Present	Present
Scleral discoloration........	A tinge of yellow	A greenish tinge	A greenish tint	A peculiar greenish hue	Greenish yellow	Greenish yellow
Dyspnea on exertion........	For about 1 year	For five years	Present, duration not mentioned	Not mentioned	For two years	Not present
Cardiac enlargement.......	Present	Present	Not mentioned	Present	Present	Present
Splenic enlargement........	Absent	Absent	Absent	Absent	Absent, spleen weighed 8 gm.	Present (malaria, 7 mo. previously)
Abdominal pain............	Epigastric pain	Pain and tenderness over spleen	Not mentioned	Pain in upper abdomen	Upper abdominal pain	Epigastric pain with vomiting
Muscle and joint pains.....	Muscular and arthritic pains	No pains, but swelling of wrists and ankles	Rheumatic pains for years	Not mentioned	Pains in all large joints	Absent
Urinary findings...........	Albumin, casts, trace of bile	Pus and casts, bile present	Not mentioned	Albumin, casts, bile present	Casts, urobilin present	Casts, urobilin present
Wassermann reaction......	Not in use	No record	Negative	Negative	Negative	Negative
Malaria....................	Negative	Negative	Negative	Negative	Negative	Negative
Stools......................	Negative	Negative	Negative	Negative	Negative	Negative
Blood culture..............	No record	No record	No growth	No growth	Negative	Negative
Sickle cells or "latent sickling" in blood of other members of family	No examination	No examination	Father's blood showed "latent sickling"	No examination	Paternal grandfather, father and one brother show "latent sickling," two brothers have sickle cells	Father, mother and two sisters have "latent sickling"; no other members of family examined

for variable periods of time at room temperature. Guthrie and Huck[6] refer to the presence of sickles in the blood of a number of relatives of their patient. In the family of our Case 1, the paternal grandfather, the father and one brother showed "latent sickling" as described by Emmel;[5] while two brothers presented the typical blood picture of sickle-cell anemia. One of these brothers, in fact, presented the entire group of symptoms which we have outlined above, to a more striking degree than the patient himself. All the members of this family who presented the sickle-cell phenomenon had greenish yellow sclerae (quite different from the "muddy" discoloration so common in negroes), general glandular enlargement and absence of splenomegaly, and three gave a history of recurrent abdominal pain. In the family of our Case 2, both the father and mother showed "latent sickling," as did two of the sisters. All showed the characteristic scleral discoloration and general glandular enlargement. No other members of the family could be examined owing to superstitious fears aroused by our interest in their blood.

As all the reported cases of sickle-cell anemia have developed in adults and no necropsy has been recorded in the literature, we present in considerable detail two cases occurring in children.

REPORT OF CASES

Case 1.—*History.*—A. C., a boy, negro (pure blood), aged 5 years and 7 months, entered the University Hospital, Aug. 23, 1922, complaining of general rigidity of body, arms and legs, with frequently recurring painful tonic spasms, and frequent attacks of abdominal pain localized in the epigastrium. The grandfather on the father's side was living and apparently well. The grandmother died from an unknown cause many years ago. There were no data obtainable as to the maternal grandparents. The father and mother were living and healthy. Both had had malaria in childhood. There was no history of syphilis. There had been one miscarriage at three months, the second pregnancy. Of five siblings, one sister (aged 5 days) died of hemorrhagic disease of new-born (bled to death from navel). A brother, aged 11, was in good health but tired easily and was somewhat breathless after exertion. A brother, aged 8, was not well. Four years previously, he had many swollen joints, with pain and tenderness, tired easily, was short of breath on slight exertion and had frequent attacks of abdominal pain. A brother, aged 4, was apparently well, and a sister, aged 20 months, was well. There was no history of usual diseases believed to show familial tendency.

A. C., a full term baby, born with normal delivery, weight 8 pounds (3,630 gm.), developed normally throughout infancy. He was breast fed for one year, but after the sixth month was given additional feeding of almost anything on the family table, notably cabbage "pot liquor." Since the age of 1 year, he had eaten practically everything he could lay his hands on, including dirt, plaster, clay, paint off the side of the house and grass. He frequently chewed shoe strings. In spite of these exceptional dietary vagaries, he was, so his mother said, a strong, healthy child up to 2 years of age. There was no history of measles, pertussis, chickenpox, smallpox, scarlet fever, diphtheria, congenital syphilis or ground itch.

Two years before, an "irregular" physician, without physical examination or blood examination, stated that the patient had malarial fever. He was in bed about one month, and was at times delirious, at other times stuporous. After he was out of bed, his mind was clear, but his left arm and left leg were weak. The left arm was spastic and flexed at the elbow; the left leg was spastic and tripped him in walking (probably poliencephalitis). After being up about two weeks, he began to vomit and had pains in upper abdomen. A few days later, his feet began to swell. Pains developed in the shoulders, elbows, wrists, knees and ankles, and were followed in a few days by swelling in the joints. He soon began to complain of shortness of breath on exertion. These symptoms had all been present more or less constantly up to the onset of the present illness. For the past six months, the mother said, the child had complained at times of pains in the ears and difficulty in hearing, although there had never been any discharge from the ears.

Six weeks before, the patient began to complain of more than usual disability; wished to lie down all the time; had frequent vomiting, with almost constant high abdominal pain, and was markedly constipated. Two weeks later, the stiffness of the joints on the left side of the body became more marked, all the large joints being involved. Following this, the corresponding joints of the right side gradually became affected, and, for the past four weeks, the patient has suffered great pain when turned in bed. Two weeks ago, there was a sudden onset of painful tonic spasms, at first occurring every six to eight hours but increasing in frequency until, at the time of examination, there was one nearly every hour. These were frequently precipitated by moving or handling the patient. There had been marked mental dulness since the onset of the spasms. There had been no trismus.

Physical Examination.—The temperature was 98 F.; pulse, 102; respiration rate, 20; blood pressure, 118 systolic and 50 diastolic.

The patient was poorly nourished and underdeveloped. When not in tonic spasm, he lay quietly in bed, apparently in considerable pain. The mental condition was poor, and one gained the impression that this was a case of meningitis. The forearms were flexed on the arms, the fingers, flexed over the thumbs; the legs were extended, and the entire left side exhibited more spasticity than the right. The skin was dry and loose.

The head was normal in shape and size, with no exostoses or other bony prominences. The fontanels were closed. The eyes showed moderate exophthalmos, but there is no gross evidence of disturbance of the extra-ocular muscles. The conjunctivae were pale, and the sclerae showed a uniform deep greenish-yellow discoloration. The pupils were round, not dilated, equal in size and reacted to light. Ophthalmoscopic examination revealed no abnormalities aside from marked anemia. The ears were negative on external and otoscopic examination. The nose showed nothing abnormal. The mucous membranes of the mouth were very pale; the tongue was coated; the teeth showed caries, and the tonsils were large, with many large crypts. The pharynx was negative.

Examination of the neck revealed marked enlargement of the posterior cervical glands. The thyroid was negative.

The axillary, epithrochlear and inguinal glands were enlarged and firm.

The thorax showed normal conformation and equal expansion. The respiratory movements were good. The lungs were negative throughout on percussion and auscultation.

Examination of the heart revealed: apex beat in fifth interspace, 1.5 cm. outside the midclavicular line; no shocks or thrills over the precordium; relative dulness extending 3 cm. to the left of the midclavicular line in the fifth interspace, 2.5 cm. to the right of the sternal margin in the fourth interspace. The heart sounds in the mitral area were of fair quality. There was a prolonged blowing systolic murmur audible over the entire precordium, with intensification in the mitral and pulmonic areas. The pulmonic second sound was accentuated.

The abdomen appeared to be normal. The liver, spleen and kidneys were not palpated. There was no rigidity or muscle spasm.

The genitalia and the extremities were negative.

Tests of the reflexes revealed: biceps, triceps and periosteoradial, hyperactive, more on the left than the right; abdominal and cremasteric, present; knee jerks and ankle jerks, markedly exaggerated, with no clonus; Kernig, positive; Babinsky, Oppenheim and Gordon, negative; Trousseau and Chvostek, negative. There was no opisthotonus.

During a spasm, there was moderate retraction of the head, the jaws were fixed and the arms were held close to the body, with the fore arms and hands tightly flexed. The trunk muscles were rigid without true opisthotonus. The thighs and legs were rigidly extended.

Laboratory Examinations.—The urine was clear, amber, with a specific gravity of 1.005; acid, and reacting negatively to tests for albumin, sugar, acetone and diacetic acid and bile. The test for urobilin was strongly positive. Microscopic examination revealed a few hyaline and granular casts.

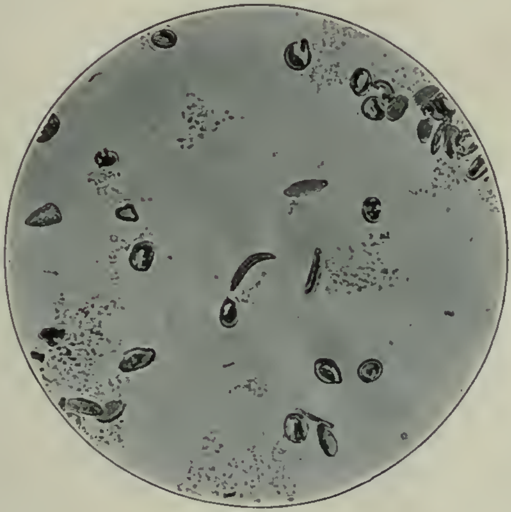

Fig. 1 (Case 1, A. C.).—Fresh blood preparation; × 600.

The stool was negative for blood, ova and parasites.

Blood examination revealed: erythrocytes, 1,328,000; hemoglobin, (Dare) 25 per cent.; leukocytes, 64,000; color index 0.9; differential count: 1.000 cells; neutrophils, 78.1 per cent.; eosinophils, 0.9 per cent.; basophils, 0.1 per cent.; large mononuclears, 2.6 per cent.; small mononuclears, 13.5 per cent.; large lymphocytes, 0.9 per cent.; transitionals, 1.9 per cent.; myelocytes, 0.5 per cent.; myeloblasts, 0.4 per cent.; unidentified, 0.7 per cent.

Particular interest centered around the blood. While making the red count, it was noted that a number of the erythrocytes in the counting chamber were tenuous, oat shaped and "sickle" shaped. Examination of a stained smear confirmed the impression already formed of the character of the blood. The salient characteristics of the erythrocytes as seen in the stained smears were as follows: 1. There were a large number (about 20 per cent.) of sickle-shaped and elongated red blood cells. There was great variation in the size of these cells, some being so small as to suggest fragments of cells, others attaining a length of from 13 to 14 microns and a width of from 2 to 4 microns. These erythrocytes, when narrow, stained deeply and evenly; when wide, there was often a pale area in the middle, comparable to that seen in the red cells in secondary anemias. 2. The approximately normal shaped cells, which made up four fifths of the total red count, presented the appearance which is associated with severe secondary anemia. There was marked anisocytosis, the microcytes as a rule staining deeply, while the macrocytes and normocytes tended to be pale, with marked central pallor. There were many cells showing diffuse basophilia. Punctate basophilia was not noted. 3. Nucleated red blood cells were seen in all preparations that were examined. As a rule, these were typical normoblasts. A few intermediates with megaloblastic nuclei were seen, but no typical megaloblasts. No nucleated sickle cells were seen.

In practically all of the stained smears, there were occasional large mononuclear leukocytes which had engulfed erythrocytes. The number of these phagocytes varied greatly from day to day. On some occasions, cells were seen which had as many as three red cell inclusions.

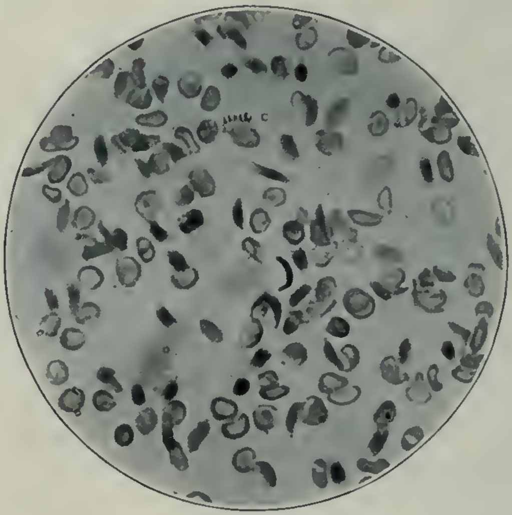

Fig. 2 (Case 1, A. C.).—Stained blood smear; × 600.

The blood platelets presented no abnormalities in number or structure. The leukocytes presented some points worthy of note. Many of the neutrophils showed an extraordinary degree of lobulation of the nuclei, seven and eight lobes being seen in many of them. In addition, many of them presented the nuclear excrescences noted by Emmel.

The absolute number of eosinophils was much increased, although the percentage ratio was not above normal. No unusual lobulation of the nuclei of the eosinophils was noted, nor were there any nuclear excrescences. The number of immature leukocytes of myelogenous origin was not greater than would be expected in a leukocytosis of this grade in a child of 6.

The fresh blood showed the same degree of sickling and anisocytosis that was observed in the stained smears. It presented other peculiarities which will be described at length below. Smears of the patient's blood stained with brilliant cresyl blue showed from 15 to 24 per cent. of reticulocytes on various occasions. It was noted that only a small number of the sickle cells showed reticulation. The resistance of the erythrocytes to hypotonic salt solutions was tested and found to show no variation from the normal. Hemolysis began at 0.45 and was complete at 0.26.

The serum of this patient when collected with all precautions against hemolysis was a brilliant lemon yellow. Unfortunately, no effort to determine urobilin in the serum was made.

The blood sugar was normal, 100 mg. per hundred cubic centimeters of blood. The Wassermann reaction was negative on two occasions. The patient's blood belonged to Group IV (Moss classification). The two transfusions which he received were without effect on the blood picture and were unaccompanied by any objective signs of reaction.

Lumbar puncture was done on the day of admission and again four days later. The fluid was clear on both occasions; there was no globulin, and the cell count was four and six. The Wassermann and colloidal gold tests were negative.

Course in Hospital.—Treatment was directed toward the recurrent spasms, and an effort was made to improve the general condition by the transfusion of blood. The temperature did not go above 102 F. at any time. The patient's condition grew steadily worse, without any satisfactory cause for the convulsions being discovered. Death occurred during a spasm on the eighth day under observation.

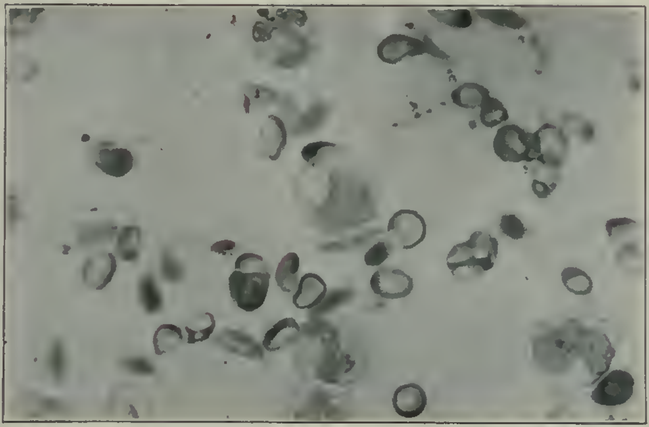

Fig. 3 (Case 1, A. C.).—Stained blood smear, showing large mononuclear phagocyte with red cell inclusion; × 900.

Necropsy Findings (Dr. Lichenstein).—Necropsy was performed two hours after death. The body was 100 cm. long; weight 20 kg. The skin was smooth. Rigor was absent. The pupils were moderately dilated, even and equal. The sclerae were decidedly greenish-yellow. The visible mucosa was extremely pale. Examination of the extremities revealed nothing noteworthy.

The thymus gland was disproportionately large for the age. Both pleural cavities contained a few slight adhesions. Examination of the lungs revealed nothing noteworthy besides pallor. The pericardial cavity contained a slight excess of clear fluid. The heart was pale, and was increased nearly twice in size, particularly from an hyperthrophy of the left side. The right side contained clotted blood. Examination of the endocardium, the valves and the aorta revealed nothing unusual. The heart weighed 120 gm.

The liver extended 5 cm. below the costal margin, and was large, pale and somewhat greasy. There were no apparent changes in structure. The weight was 690 gm.

The spleen which was very small and was increased in consistency, measured 5 by 3 by 1 to 2 cm. Weight was 7.9 gm. The malpighian bodies were barely visible. The pulp was diminished, and many small dark red blotches were scattered throughout.

The pancreas measured 15 by 3 by 2 to 3 cm. There were no gross changes.

The kidneys were also increased in size, pale, considerably increased in consistency and finely scarred over their surfaces and throughout the cortex. The cut surface was rather cloudy and after fixation in formaldehyd a fine yellowish red stippling was seen throughout the cortex and the columns of Bertini.

Examination of the stomach, intestines and genitalia revealed nothing noteworthy. The mesenteric lymph nodes were enlarged from hyperplasia. The bone marrow from femur and ribs was bright red and of normal consistency.

Microscopic Notes (Dr. Lamar).—Liver: The cords were rather swollen and the cells more granular than usual and poorly defined in outline. There were numerous small scattered areas of fine dark brown pigmentation of the liver cells, apparently bile imbibition.

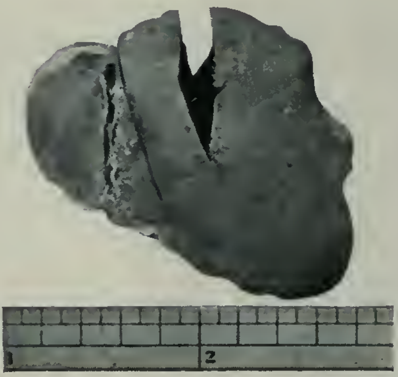

Fig. 4 (Case 1, A. C.).—Spleen; actual size.

Spleen: The capsule was slightly thickened and uneven from an occasional depression; the trabeculae were conspicuously large; the parenchyma was much reduced in amount, and the malpighian bodies were inconspicuous, ill-defined and distorted in outline. The blood, of which there is much, was most unevenly distributed in large and smaller areas of extreme congestion where the parenchyma was reduced. Besides, there were many small and large actual hemorrhages scattered throughout; some recent, others older, and the pigmented scars of others still older (Berlin blue reaction). To summarize, the spleen presented congestion, hemorrhages, scarring and marked atrophy (aplasia?) .

Kidneys: The kidneys showed alike an uneven capsular line from numerous small depressions. The glomeruli were strikingly prominent and distended by blood, much of which was agglutinated. The nuclei in some glomeruli were increased twice in number, and there was pericapsular fibrosis in some glomeruli. Many of the convoluted tubules were dilated; most of them contained a granular precipitate, and a few contained casts. Generally, the epithelial cells showed cloudy swelling. Here and there, there were necrobiotic changes and occasional desquamation. Many epithelial cells, in smaller and larger groups throughout the sections, contain much fine and coarsely granular yellowish brown pigment. Indeed, the cells of some tubules were laden with this pigment, which does not give the iron reaction.

Beneath the capsule and scattered elsewhere throughout the section, even to some extent in the medulla, were small areas of recent fibrosis where some tubules were lacking and others were compressed. About some of these areas were small accumulations of mononuclear and polymorphonuclear leukocytes.

Mesenteric lymph nodes: These showed much diffuse hyperplasia.

Bone marrow: The femur contained a large number of sickle-shaped red blood cells, often in large clusters between the capillaries and sometimes within them. There was much brownish black pigment in fine and coarse granules, mainly extracellular, but also, to some extent, within large mononuclear cells.

In all the various sections of the organs, many sickle-shaped red blood cells were seen within the capillaries.

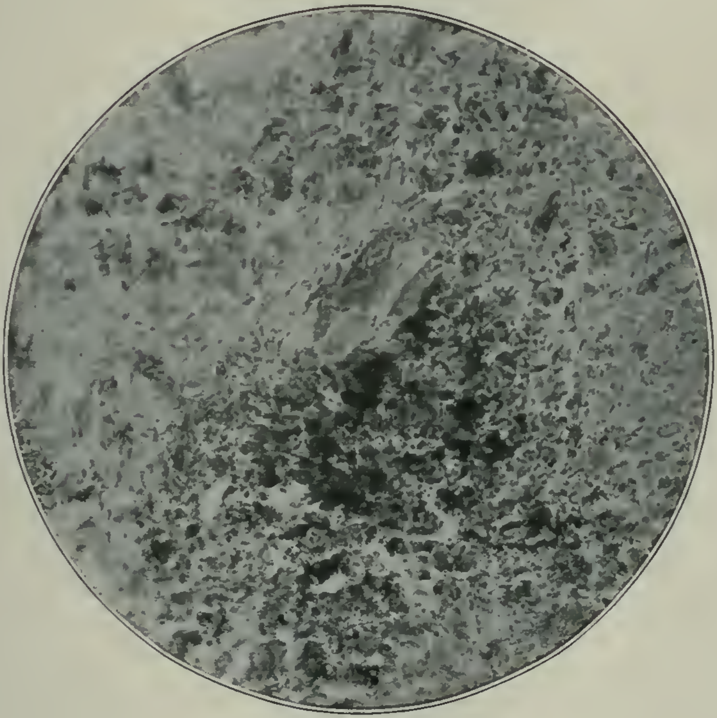

Fig. 5 (Case 1, A. C.).—Section of spleen, showing fresh hemorrhage; × 400.

Pathologic diagnosis: A diagnosis was made of emaciation, anemia, parenchymatous nephritis (subacute); hypertrophy of heart, atrophy or aplasia of spleen, repeated hemorrhages, fibrosis; pigmentation of sclerae; pigmentation, iron-free, of kidneys; enlarged thymus; mesenteric lymphatic hyperplasia; slight pleural adhesions; sickle-shaped red blood cells.

Smears from the marrow of ribs and femur were stained with Wright's stain. These preparations were of special interest. The white cells presented no particular abnormalities aside from those compatible with increased activity of the marrow, myeloblasts and immature myelocytes being present in large numbers. The erythrocytic elements, however, were strikingly abnormal and differ from any that we can find described. The abnormal types of red blood cells can be divided into three groups:

1. Sickle and oat shaped cells similar in all respects to those found in the peripheral blood, but relatively much more numerous. These showed varia-

tions in size even more pronounced than those seen in blood smears, and polychromatophilia was frequent. Erythroblasts presenting these forms were common. The nuclei of these nucleated sickle cells were uniformly of the dense normoblastic type and varied much in size. Usually, the nucleus was round and occupied the middle of the cell. Occasionally, forms were seen (Fig. 7 *a*) in which the nucleus was elongated in the direction of the long axis of the cell.

2. Filiform erythrocytes, the length of which was six to twenty times the width. These cells presented the most bizarre forms and the greatest variation in size (Fig. 8). Some were so small as to suggest bacillary forms. These were probably fragments. Many were between 10 and 15 microns long with a diameter of 0.5 micron (Fig. 7 *c*). The most striking types were the extremely long forms running up to 40 microns in length, varying in width from 1 to 5 microns. Many of these large forms presented enlargements at one end, giving them a club shape (Fig. 9). Others were larger at both ends than in the middle. Still others showed excrescences at various points. These filiform cells occurred singly and in clusters. Occasional groups having a radial arrangement were seen. These cells were the most striking feature of the picture, forming a network over the entire smear. It was thought at first that trauma might have to do with their extreme tenuosity, but sections showed masses of the same type of cells in the intercapillary spaces.

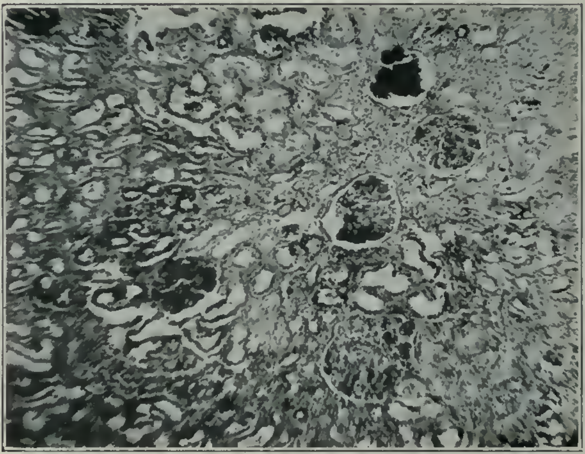

Fig. 6 (Case 1, A. C.).—Section of kidney cortex.

Nucleated cells corresponding to these forms were of frequent occurrence (Figs. 7, 8 and 9). The nuclei of these usually occurred in or near one end of the cell, and were surrounded by a thin layer of cytoplasm. Nuclear extrusion, possibly the result of trauma, was a frequent phenomenon. The nuclei of these cells too were always of the normoblastic type, and usually very dense.

3. Erythrocytes and erythroblasts of no fixed shape or size. These were quite common, and only a poor idea of their variety is given by the figures. Some were large, as much as 20 microns in their greatest diameter, and in shape suggested masses of hemoglobin-containing tissue torn away from a mother lump. These large cells were frequently very irregular in staining qualities.

Nucleated forms corresponding to these were seen. A few presented the megaloblastic type of nucleus but the majority were normoblastic.

These abnormal forms by no means made up the entire erythrocytic content of the marrow. All the normal types of erythroblasts were present in large numbers, and about 60 per cent. of the erythrocytes were circular in outline but showed great variations in size.

Smears from the splenic pulp were also stained with Wright's stain. The only striking abnormality noted was the preponderance of sickle cells. From 50 to 60 per cent. of the red cells present were sickle or oat shaped. It is of interest that no evidence of phagocytosis of red cells was seen in any of the large mononuclear elements from the spleen.

Case 2.—*History.*—R. R., boy, negro (pure blood), aged 6 years, entered the University Hospital, Feb. 9, 1923, complaining of headache, pains in the stomach, general weakness and jaundice. The grandparents were all dead, of unknown causes. The father, aged 40, and the mother, aged 38, were living and well. Both had had malaria repeatedly. There was no history of syphilis. Four brothers and five sisters were all living and well. There were no miscarriages. No history was elicited of the usual diseases believed to indicate a familial tendency.

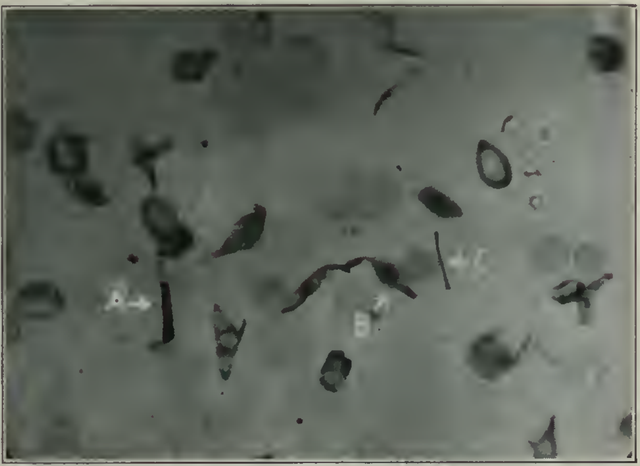

Fig. 7 (Case 1, A. C.).—*a,* sickle cell with elongated nucleus; *b,* bizarre erythroblast of spindle type; *c,* minute filiform erythrocyte.

The patient was a normal full-term baby, of a normal delivery, breast fed for ten months and then bottle fed, with the addition of various articles of diet. He was always perfectly well up to August, 1922, at which time there was a severe attack of malaria for which the patient was treated in the outpatient department. Plasmodia were found at this time, but no note was made of any abnormality of the blood.

The present illness began three weeks before, with headache and recurring attacks of abdominal pain referred to the epigastrium and left hypochondrium. There was no constipation or diarrhea. Headache had been constant. Attacks of abdominal pain occurred at intervals of two or three days, often occompanied by vomiting. Three days after onset, the mother noticed that the sclerae were slightly yellow. This jaundice had increased only slightly since. There had been no itching of the skin. There had been no dyspnea, but extreme lassitude.

Physical Examination.—The temperature was 101.4 F.; pulse, 120; respiration rate, 28; blood pressure, systolic 100, diastolic, 40. The patient was of good bony and muscular development and fairly well nourished. The skin was "gingerbread" color, with a definite suggestion of jaundice, particularly on the palms and soles. There was no rash. Slight edema of the ankles was noted. There was no evidence of rickets or congenital syphilis.

The head was of normal contour. The hair was sparse for a negro and had a peculiar reddish cast. There was no tenderness over the mastoids. The ears were normal on external and otoscopic examination. The eyes showed nothing abnormal except a very marked greenish yellow discoloration of the sclerae. The mucous membranes were very pale. The teeth were good; the tongue was pale and slightly coated; the tonsils were large but not inflamed.

The neck showed nothing abnormal. The glands, cervical, axillary, epitrochlear and inguinal, showed marked enlargement. The thorax was well formed. The left costal margin flared slightly as compared with the right. The respiratory movements were good. The lungs were resonant throughout on percussion, but on auscultation there are very many moist râles of all sizes over both sides of the back, more numerous as the bases were approached. There were no significant changes in the breath sounds.

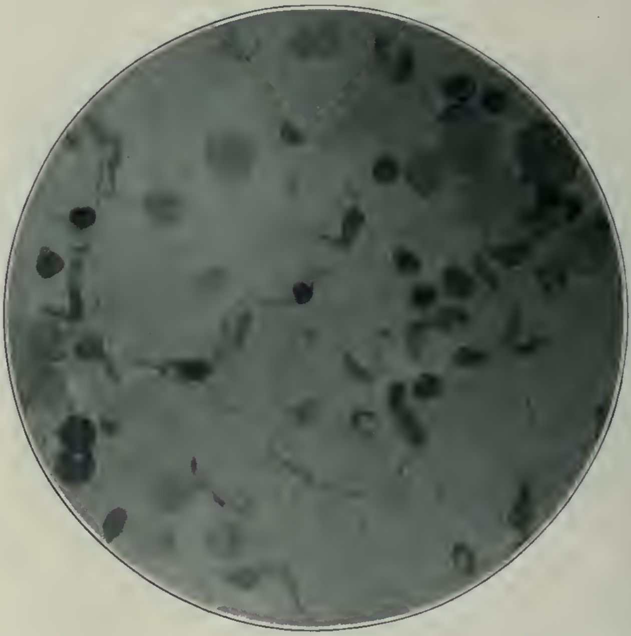

Fig. 8 (Case 1, A. C.).—Smear from bone marrow, showing various types of abnormal erythrocytes.

Examination of the heart revealed the apex beat in the fifth interspace in the midclavicular line. No thrill or shock was noted. Dulness extended 3 cm. outside the nipple line on the left. There was no increase on the right. The sounds were of fair quality. There was a loud blowing systolic murmur at the apex; and over the pulmonic areas, the pulmonic second sound was quite loud.

The abdomen was distended in the upper portion, where the liver was felt four finger-breadths below the costal margin, and the spleen on the left side could be felt two finger-breadths below the costal margin. The spleen was hard, its edge thick and round. The kidneys were not felt. Examination of the genitalia revealed nothing noteworthy.

The reflexes were all normal.

To summarize: Jaundice, hypertrophied tonsils, physical signs of bronchitis, enlarged heart with systolic murmurs at mitral and pulmonic areas, marked enlargement of liver and spleen and severe anemia were noted.

Laboratory Examinations.—The urine was dark brown, clear, acid, with a specific gravity of 1.010, and negative for albumin sugar, acetone and diacetic acid and bile. Tests for urobilin were strongly positive. The stools were negative for blood, parasites and ova. Blood examination revealed: erythrocytes, 1,544,000; hemoglobin, 38 per cent. (Dare); leukocytes, 20,000; color index, 1.2; differential count (500 cells): neutrophils, 33.0 per cent.; eosinophils, 2.2 per cent.; basophils, 0.6 per cent.; large mononuclears, 9.0 per cent.; small mononuclears, 48.6 per cent.; large lymphocytes, 0.8 per cent.; transitionals, 4.0 per cent.; myelocytes, 0.8 per cent.; unidentified, 0.6 per cent. Seventy nucleated red cells were seen. The platelets were normal in numbers and size.

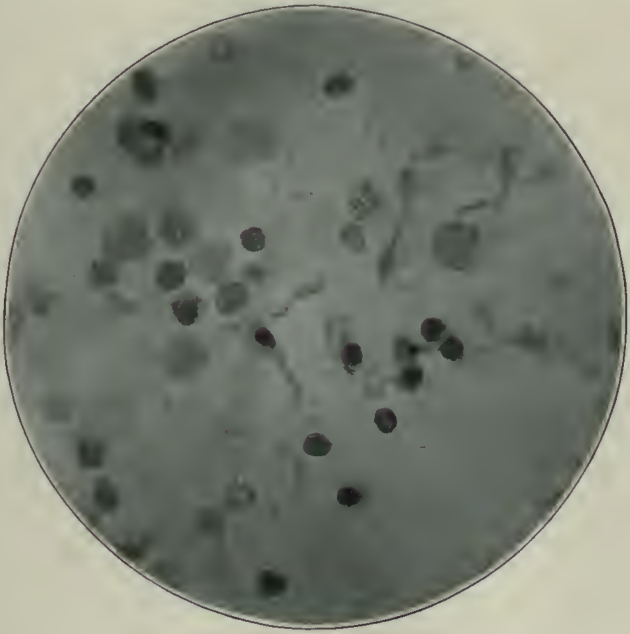

Fig. 9 (Case 1, A. C.).—Smear from bone marrow, showing club-shaped erythroblast.

The blood smear presented the typical picture of sickle-cell anemia. Twenty-seven per cent. of the erythrocytes were sickle-cells (Fig. 10). Two nucleated sickle-cells were seen. There was no evidence of malaria. The fresh blood showed the same characteristics as the smears, together with other peculiarities which will be described below.

The smears stained with brilliant cresyl blue showed 34 per cent. reticulocytes. The resistance of the erythrocytes to hypotonic salt solutions was normal. Hemolysis began at 0.45 and was complete at 0.24.

The serum was a deep canary yellow when collected with all precautions against hemolysis. The blood sugar was normal. The Wassermann reaction was negative. The patient's blood belonged to Group II (Moss classification).

More detailed examination of the stained smears of the blood confirmed the first impression that it presented the typical picture of sickle cell anemia. The variations in size and shape were the same as in Case 1. Phagocytes containing erythrocytes were somewhat more numerous in the blood than in that of Case 1, and on the first day in the hospital the smears showed several nucleated cells presenting the characteristic sickle shape and deep staining reaction. Nucleated sickle cells have not been described in any of the reported cases and were not found in the peripheral blood of our Case 1.

This patient remained in the hospital for eleven days, during which time many tests of the blood were made. There was no significant change in the red or white cell counts, and the differential count showed no marked variations. Malaria and intestinal parasites were searched for daily, with negative results. Roentgen-ray examination of the chest revealed some general diffuse haziness of the lung shadows. The heart was described as much enlarged, mainly from left ventricular hypertrophy. The Pirquet test and the intradermal tuberculin tests were negative on two occasions. Splenic puncture was not attempted owing to objections by the family. The patient was discharged, clinically unimproved, on the demand of his family.

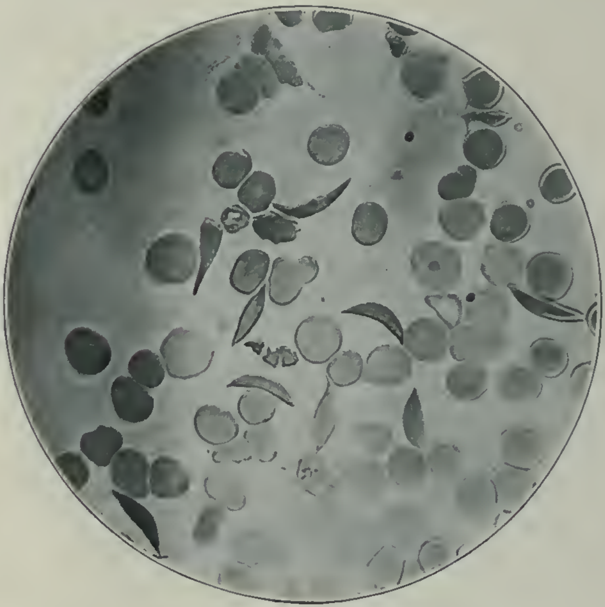

Fig. 10 (Case 2, R. R.).—Fresh blood preparation.

EXPERIMENTS WITH THE BLOOD OF THE TWO PATIENTS REPORTED AND THE BLOOD OF VARIOUS MEMBERS OF THEIR FAMILIES

An effort was made to confirm the observations of Emmel on the behavior of the fresh blood in sickle cell anemia. Parallel series of experiments were carried out on the blood of our two patients. As they were identical in all respects, the following descriptions apply to both.

Fresh coverslip preparations made on carefully cleaned glassware and sealed with hard paraffin showed rapid conversion of the circular erythrocytes into sickle forms. The sickle cells became more tenuous. This change began almost immediately, and, at room temperature, progressed until, at the end of twenty-four hours, almost all the erythrocytes had become deformed. This was not an apparent change due to hemolysis of the circular cells. Many of the shapes assumed were most bizarre, with long filamentous projections from the tips of the crescent shapes and various points on the concave margin of the sickles. The cells became darker and more "brassy" as though there were concentration of the hemoglobin. These cells were very plastic and could be distorted by pressure on the coverslip, but always returned to the original shape when the pressure was removed. Crenation sometimes occurred, but was strikingly abnormal, each little excresence being prolonged into a filamentous projection. Phagocytosis went on very actively in these sealed preparations. The large mononuclear leukocytes were apparently the only type of white cell exhibiting phagocytic activity.

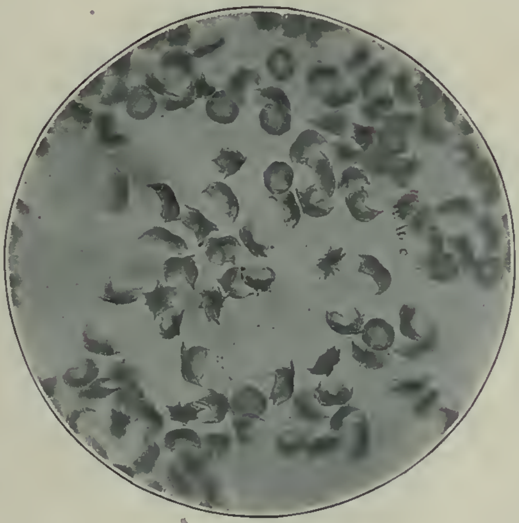

Fig. 11 (Case 1, C. C.).—Fresh blood preparation, showing "sickling" after five hours.

Washed cells from the patients, mixed with centrifuged compatible serum from normal individuals, underwent the same changes at practically the same rate of speed as in the patient's own serum. This experiment was repeated with serums from patients suffering from a variety of diseases. Bile or bile pigments in the serums definitely accelerated the sickling. This was noted both in serums from patients with biliary obstruction and in those with which minute amounts of bile had been mixed. Sodium glycocholate in extremely high dilution also accelerated the changes. Inactivated serums had practically the same effect as unheated ones, no definite difference in the time necessary to produce maximal sickling being noted. Serum is essential to the change, however. The patients' cells, suspended in 0.85 per cent. sodium chlorid, Locke's solution and isotonic glucose solutions, underwent no changes even after the lapse of a week. In these mediums, normal crenation frequently occurred after forty-eight hours.

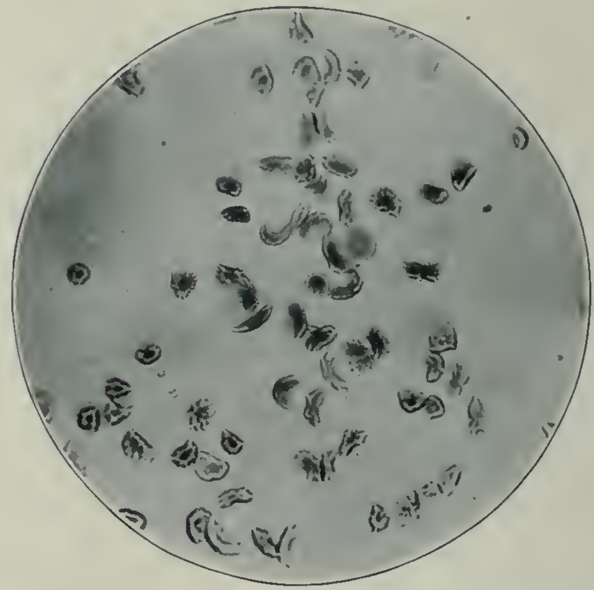

Fig. 12 (Case 1, W. C. [father]).—Fresh blood preparation, showing sickling after twelve hours.

Efforts to produce sickling in compatible cells of other individuals by mixing them with the patients' serums were without success. This experiment was performed with the cells of twenty individuals in each case, and nothing suggesting sickling was seen.

It was found that cold definitely inhibited the change. Preparations of the patients' blood placed in the icebox could be kept until hemolysis began without any increase in the number of sickle cells present. Heat, on the contrary, speeded up the process very definitely. Preparations kept in the incubator showed maximal sickling at the end of four hours.

Considerable interest was aroused by the active phagocytosis which was noted in the fresh preparations. Experiments were carried out in an effort to produce similar phagocytosis of normal erythrocytes by the patients' leukocytes. Washed leukocytes from the patients were mixed with washed compatible erythrocytes in the patients' serums and in normal compatible serums. No phagocytosis was observed. Also, washed normal leukocytes from compatible blood were mixed with the patients erythrocytes in their own and in normal serums, and no phagocytosis took place.

Following the suggestion of Emmel and of Guthrie and Huck, the blood specimens of all the available members of the patient's families were examined. In addition, note was taken of the color of the sclerae, the condition of the superficial lymph glands and the size of the spleen. These results are presented in Tables 2 and 3.

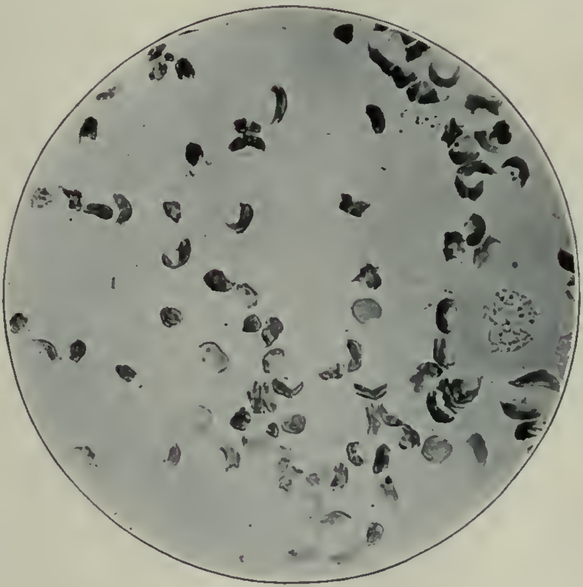

Fig. 13 (Case 1, J. C.).—Fresh blood preparation, showing sickle cells immediately after making preparation.

In Case 1, eight members of the family were examined. The paternal grandfather, C. C., aged 65, showed marked general glandular enlargement and greenish yellow sclerae. The spleen was not palpable. The blood showed no anemia and the fresh blood showed no sickle cells. After four hours, there was marked sickling, which became almost complete in twenty-four hours (Fig. 11). The father, W. C., aged 34, had yellow sclerae and marked general glandular enlargement. The spleen was not felt. The blood showed no abnormality in smears. The fresh preparations showed the typical sickle deformity in eighteen hours

(Fig. 12). The paternal uncle, T. C., aged 40, had white sclerae, but no general glandular enlargement and no splenomegaly. His blood was normal in all respects. The mother, M. C., aged 32, showed nothing abnormal in either physical or blood examination. The oldest brother, W. C., aged 11, had greenish sclerae and general glandular enlargement, but no splenomegaly. The blood showed a moderate secondary anemia with marked poikilocytosis. The fresh preparations showed marked sickling in four hours. The second brother, J. C., aged 8, had dyspnea on exertion and intermittent attacks of "colic," and was weak and indolent. He had deep greenish-yellow sclerae and general glandular enlargement, but no splenomegaly. His blood showed a marked anemia, with a more striking picture of sickle-cell anemia than that of his brother A. C. (Fig. 13). The third brother, R. C., aged 23 months

TABLE 2.—*Blood Findings in Family of Case 1*

	C. C. (Grand-father)	W. C. (Father)	W. C. (Brother)	J. C. (Brother)	A. C. (Patient)	R. C. (Brother)
Erythrocytes	4,312,000	5,240,000	3,560,000	2,056,000	1,328 000	3,662,000
Hemoblobin	75%	74%	70%	34%	25%	68%
Leukocytes	6,700	7,360	7,600	16,900	64.000	8,240
Sickle cells	4 hours	6 hours	4 hours	35%	20%	11%
Reticulocytes	....	....	....	18%	15.4%	....
Nucleated erythrocytes	None	None	None	Many	Many	Few
Neutrophils	46.4%	51.6%	35.6%	52.33%	78.1%	28.0%
Eosinophils	8.8%	4.8%	16.0%	3.00%	0.9%	3.0%
Basophils	2.4%	0.4%	0.0	0.66%	0.1%	0.0
Large mononuclears	8.0%	12.2%	8.0%	8.33%	2.6%	12.0%
Small mononuclears	30.4%	2[illegible].2%	34.0%	29.60%	13.5%	50.0%
Transitionals	2.4%	2.0%	2.4%	2.33%	1.9%	6.0%
Large lymphocytes	0	0	2.4%	1.33%	0.9%	1.0%
Myelocytes	0	0	0	2.33%	0.8%	0
Unidentified	0	0	0.8%	0.33%	0.7%	0
Sclerae	Greenish	Greenish	Greenish	Greenish	Greenish	Greenish
Glands	Generally enlarged	Generally enlarged	Generally enlarged	Generally enlarged	Generally enlarged	Generally enlarged

TABLE 3.—*Blood Findings in Family of Case 2*

	J. R. (Father)	M. R. (Mother)	A. R. (Sister)	N. R. (Sister)	R. R. (Patient)
Erythrocytes	4,400,000	4,160,000	4,240,000	4,160,000	1,544,000
Hemoglobin	88%	80%	80%	80%	38%
Leukocytes	10,200	6,800	14,600	8,800	20,000
Sickle cells	12-16 hours	12-16 hours	2%	4 hours	27%
Reticulocytes	....	....	....	....	34%
Nucleated erythrocytes	None	None	None	None	Many
Neutrophils	46.8%	44.8%	36.4%	47.0%	33.0%
Eosinophils	2.4%	0.4%	2.4%	3.0%	2.2%
Basophils	0.0	0.0	0.0	1.0%	0.6%
Large mononuclears	15.0%	9.3%	22.0%	8.0%	9.0%
Small mononuclears	31.6%	42.8%	33.0%	37.0%	48.6%
Transitionals	3.6%	2.4%	5.6%	3.0%	4.8%
Myelocytes	0	0	0	0	0.8%
Unidentified	0	0.4%	0	0	0.6%
Sclerae	Greenish yellow	Slightly yellow	Greenish yellow	Greenish yellow	Dark greenish yellow
Glands	Generally enlarged	Slight enlargement	Slight enlargement	Slight enlargement	Generally enlarged
Spleen	Not palpable	Not palpable	Not palpable	Not palpable	Greatly enlarged

had greenish yellow sclerae and general glandular enlargement, but no splenomegaly. He was well. The blood showed a moderate anemia, with many sickle cells in the smears and fresh preparations. The sister, L. C., aged 10 months, was normal in all respects.

In Case 2, only four members of the family would submit to examination. These were the father and mother and two sisters, aged 13 and 11. Both the father and mother had greenish yellow sclerae; the father had marked glandular enlargement, and neither had a palpable spleen. Both had normal blood counts and smears, but both had active sickling in the fresh blood after twelve hours. (Figs. 14 and 15.) Both sisters had yellow sclerae and general glandular enlargement, with no splenic enlargement. Both had normal blood counts with the exception of a slight eosinophilia. The older sister had a few typical sickle cells in her smears (about 2 per cent.) and showed maximal sickling in six hours (Fig. 16.) The second sister had normal appearing fresh blood, but it showed maximal sickling in eighteen hours.

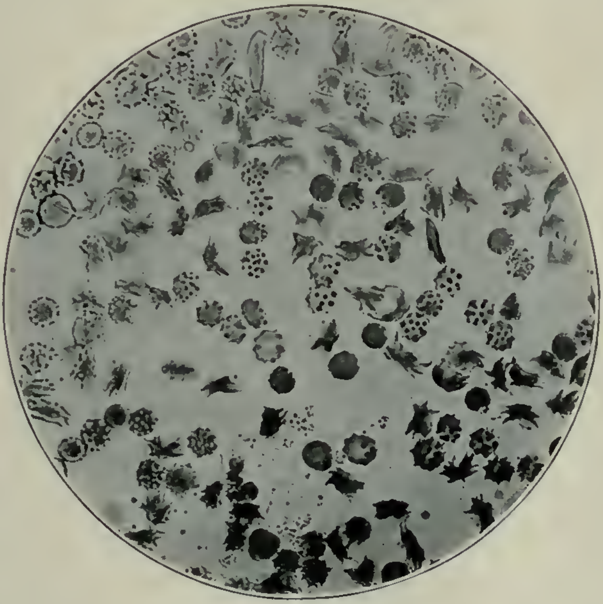

Fig. 14 (Case 2, J. R.).—Fresh blood preparation, showing sickling and crenation after eight hours.

COMMENT

The chief interest in the two cases reported lies in the necropsy findings in Case 1, and the presence, transient though it was, of nucleated sickle cells in the blood in Case 2. Previous observers, in the absence of pathologic examination of the cases and of any etiologic agent that could be discovered, have been inclined to ascribe the peculiar poikilocytosis present in this condition to changes that took place in the blood after the cells reached the peripheral circulation. The changes present in the bone marrow in Case 1 are unlike any that we found recorded. The presence in the marrow of sickle shaped, filiform and otherwise abnormal erythroblasts, with erythrocytes to correspond to these various types, seems to warrant the conclusions that the sickle cells seen in the peripheral blood are not the result of changes that go on in the circulation or in the splenic sinuses but that they are performed in the marrow as the result of some primary fault of erythropoiesis, the cause of which is as yet unknown. The presence of nucleated sickle cells in the blood in Case 2 adds some confirmation of this view.

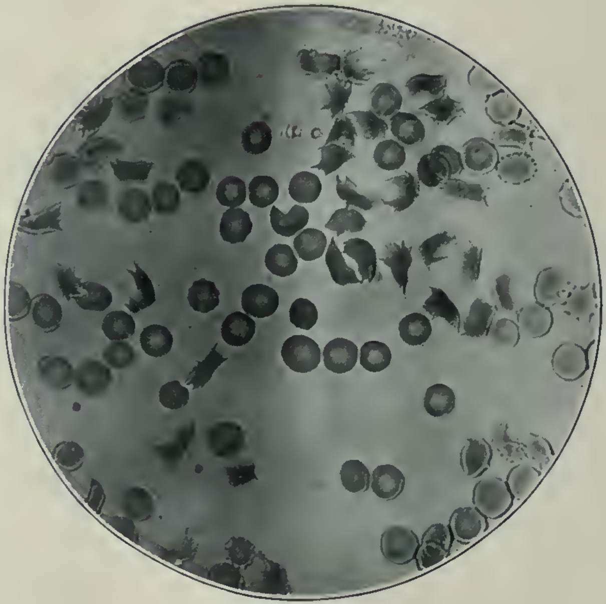

Fig. 15 (Case 2, M. R.).—Fresh blood preparation, showing sickling after eight hours.

Both our patients had attacks of high abdominal pain, localized in the epigastrium and left hypochondrium. In three of the reported cases, those of Herrick, Washburn and Mason, there were similar attacks. We lay stress on this symptom in view of the unusual findings in the spleen in Case 1. It was evident that there had been repeated hemorrhages into the spleen, and the spleen itself was greatly reduced in size. In all the reported cases, it was specifically mentioned that the spleen was not demonstrable clinically. It seems possible that the epigastric pain and perhaps the gastric disturbances were due to splenic hemorrhages.

In all the reported cases, in our cases and in the members of the families of our patients who showed "latent sickling," a peculiar scleral discoloration was present. This was not frank jaundice, but a greenish yellow pigmentation much like that seen in familial hemolytic icterus. The urine in Herrick's case showed a trace of bile; in Mason's also bile was found. Washburn's case showed bile in the urine. No mention is made of the examination in Cook and Myer's case. Both of our cases showed a heavy urobilinuria and a bright yellow serum suggesting urobilinemia. In the liver and kidneys in Case 1, there were many brown granules, in the Kuppfer cells of the liver and in the epithelium of the kidney tubules. These findings suggest most strongly that there is a hemolytic factor in the production of the anemia. Whether hemolysis is initiated by some element inherent in the blood of these individuals or whether it is dependant on extraneous factors, we are unable to state. The phagocytosis of erythrocytes in the circulating blood noted by Emmel and occurring in both our patients may have some bearing on this phase of the condition. In this connection, it may be mentioned that, in the blood of all the members of these two families who showed

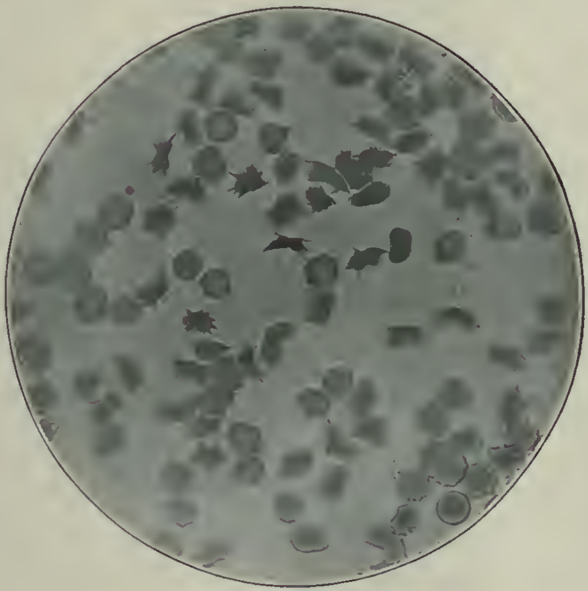

Fig. 16 (Case 2, A. R.).—Fresh blood preparation, showing sickling after four hours.

"latent sickling," there was active phagocytosis in the sealed preparations though none was noted in the stained smears of their blood.

The changes observed in the blood of the grandfather, father and oldest brother in Case 1, and in all the relatives in Case 2 who were examined, were identical with those described by Emmel in the father in the case he studied. They are also identical with the changes which go on in the blood of individuals with frank sickle cell anemia. Emmel's patient passed through a period during which her blood returned to normal so far as could be determined from stained smears, but when it was allowed to stand for four hours, many of the cells assumed the characteristic appearance found on previous examinations. We have termed this phenomenon "latent sickling," and feel that it has the same significance as the occurrence of sickle cells in the freshly smeared blood, the difference being one of degree and probably dependant on extraneous factors.

The blood of more than 300 white patients has been examined by us with special reference to "latent sickling," and in no case has anything resembling it been seen. In a similar number of negroes, it was found thirteen times, exclusive of its occurrence in the families in the cases reported. This adds weight to Mason's hypothesis that sickle cell anemia is a condition peculiar to the negro race.

SUMMARY

1. Two cases of sickle cell anemia occurring in negro children are reported.

2. Necropsy in one case revealed hitherto undescribed changes in the bone marrow which suggest that the changes in the blood are dependant on a primary defect of blood formation.

3. There is evidence that there is active hemolysis of erythrocytes in addition to disturbances in erythropoiesis.

4. Several members of the patient's family in each case showed changes in the blood analogous to those presented by the patient.

5. No similar changes in the blood of white persons has been described.

CONCLUSION

We feel warranted in stating that sickle cell anemia is a definite clinical entity, characterized by a definite symptom-complex and by specific blood findings and anatomic changes, and that it is a familial disease. There is strong evidence that it occurs only in the negro race or in persons of mixed blood.

RICKETS IN AN INFANT OF THIRTY-FOUR DAYS *

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The earliest age at which rickets begins and the precise time required for the development of the pathologic process in the bones are not definitely known. Craniotabes, the first clinical sign of involvement of the skeleton, has been described in the second month; ordinarily, however, it does not manifest itself before the third or fourth month. By the fourth month, the enlargements at the lower ends of the radius and ulna and at the costochondral junctions may have attained such size as to be recognizable on physical examinaiton, but then the rachitic process is already advanced. Craniotabes makes its appearance at a time when the pathologic process at the ends of the ribs and long bones of the extremities is in an early stage of development, and it is the earliest positive sign of rickets.

The difficulty in regard to the value of craniotabes in the diagnosis of rickets lies in the fact that defective calcification of the skull occurs in conditions other than rickets. When, however, craniotabes develops while an infant is under observation, or is widespread in the region of the lambdoidal suture, it alone justifies the diagnosis of rickets. One who relies on enlargements of the costochondral junctions for the diagnosis of early rickets will often fail to recognize the disease when present, and will believe it present when it does not exist.

Though rickets can be diagnosed by means of the roentgen ray earlier than by physical examination, it cannot be recognized by the roentgen ray at the earliest stages of its development in the bones.

The laboratory offers the means of earliest diagnosis. Rickets, as is now well known, is characterized by a disturbance in the salt equilibrium of the body. The investigations of Howland and Marriott,[1] Kramer, Tisdall and Howland,[2] which have been confirmed by numerous others, have shown that, in infantile tetany (in reality rickets accompanied or complicated by tetany), there is a diminution of the calcium in the blood serum; and investigations of Iversen and Lenstrup,[3] Howland and Kramer [4] and others have shown that, in rickets

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* From the Department of Pediatrics, Yale University School of Medicine.

1. Howland, J., and Marriott, W. McK.: Observations Upon the Calcium Content of the Blood in Infantile Tetany and Upon the Effect of Treatment by Calcium, Quart. J. Med. **11**:289, 1917-1918.

2. Kramer, Benjamin; Tisdall, F. F., and Howland, John: Observations on Infantile Tetany, Am. J. Dis. Child. **22**:431 (Nov.) 1921.

3. Iversen, P., and Lenstrup, E.: Calcium and Phosphorus in the Serum in Relation to Rickets, Forhandlingerne ved Forste Nordiske Kongres for Paediatri, 1920; cited by Howland and Kramer.

4. Howland, John, and Kramer, Benjamin: Calcium and Phosphorus in the Serum in Relation to Rickets, Am. J. Dis. Child. **22**:105 (Aug.) 1921.

unaccompanied by tetany, a diminution in the inorganic phosphorus of the blood serum is characteristic. In rickets, therefore, there may be a decrease in the calcium of the blood serum or in the inorganic phosphorus, or in both. Although information of an absolute nature is lacking, it seems probable that the changes in the salt equilibrium of the blood just mentioned precede the development of recognizable pathologic changes in the bones.

The question as to the occurrence of congenital rickets is still debated. At present, one can say merely that no reliable evidence of the occurrence of congenital rickets has ever been produced. Convincing demonstrations of rickets in the bones of new-born children have never been made. Schmorl [5] searched for rickets in the bones of 100 new-born infants, both full term and premature, but failed to find evidence of the disease in a single instance. It is probable that congenital rickets occurs rarely, if at all. There can be no doubt, however, that at birth certain children are more predisposed to the development of rickets than others. For example, premature infants and twins are more liable to develop rickets than infants born at term and born singly, and the offspring of certain families or races appear to be especially susceptible to influences which are factors in the production of rickets.

The reason for the peculiar susceptibility of the premature infant to rickets has never been explained. Hamilton [6] has recently found evidence to show that, under normal conditions, during the last three months of intra-uterine life, the fetus stores calcium in the skeleton, and, during the first few months of extra-uterine life, the normal infant draws on the store of calcium. However, he did not obtain evidence of a corresponding formation of a phosphorus depot in the last months of fetal life or a subsequent dependence on a phosphorus depot. He suggests that the peculiar susceptibility of the premature infant is due to a deficiency of stored calcium in the skeleton. The susceptibility of the premature infant to rickets may arise from the condition of immaturity of the organism and from the demands resulting from the great growth stimulus. The premature infant is not only more susceptible to rickets than the child born at term but also develops the disease at an earlier age.

The occurrence of rickets at a very early age has been reported by Schmorl,[5] Hamilton [6] and Ylppö.[7] Schmorl found rickets at

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5. Schmorl, G.: Die pathologische Anatomie der rachitischen Knochenerkrankung mit besonderer Berücksichtigung ihrer Histologie und Pathogenese, Ergebn. d. inn. Med. u. Kinderh. **4**:403, 1909.

6. Hamilton, B.: The Calcium and Phosphorus Metabolism of Prematurely Born Infants, Acta Paediat. **2**:1, 1922.

7. Ylppö, A.: Zur Physiologie, Klinik und zum Schicksal der Fruhgeborenen, Ztschr. f. Kinderh. **24**:1, 1920.

necropsy at one and one-half months. Apparently, no clinical evidences of the disease were present. Hamilton observed the development of rickets, as evidenced by craniotabes, in two premature infants during the sixth week of life. Ylppö reported rickets in a premature infant aged one and one-half months.

The case of rickets here reported is of unusual interest on account of the advanced stage which the disease had attained at an extremely early age.

REPORT OF CASE

History.—M. G., an Italian, born June 11, 1922, was admitted to the New Haven Hospital, July 15, at the age of 34 days. The father was well. The mother, who was 34 years old, had marked scoliosis and developed a "weakness of the extremities" and pains in the legs which forced her to remain in bed during the last three months of pregnancy. A roentgenogram of her spine (Fig. 5), taken on admission to the lying-in hospital, revealed a marked degree of scoliosis and rarefaction of the vcrebral column, humerous and ribs. Though a diagnosis of osteomalacia could not be made from the roentgenogram alone, it seems altogether probable that the mother was suffering from osteomalacia at the time the infant was born. There had been seven previous pregnancies, and all the children were living and well.

The diet of the mother, until about one month before the birth of the child, was most defective, consisting chiefly of milk, potatoes, macaroni and bread. The value of this diet per day was estimated to be about 1,846 calories: the calcium, per hundred grams of food, 0.6 gm.; the phosphorus, 1.2 gm. (average normal, calories, 3,000; calcium, 0.45 gm.; phosphorus, 0.88 gm.). The mother spent the last month of pregnancy in the hospital and ate the ordinary hospital fare.

The home conditions were poor. The family, consisting of eight persons, occupied three rooms on the first floor of a dark and dirty brick tenement. One bedroom had two windows on the east, another two windows on the north side. The kitchen also had two windows on the north side. The northern exposure, however, was not of great value because the light was cut off by a high building close by. The house was extremely dirty, dark and damp.

According to the mother's calculation, the patient was born two months prematurely. The birth weight of 3,260 grams (recorded at hospital) indicates that the child was born at term. No abnormalities were noted at birth. It is believed that the baby was breast fed for a few days, then given a supplementary formula. Later, it was fed entirely on a formula which was a mixture of whole milk, water and sugar, the exact composition being unknown.

Examination.—On admission to the New Haven Hospital (at the age 34 days), the infant was small and poorly nourished. The circumference of the head was 36 cm.; chest, 32.2 cm.; abdomen, 32.5 cm.; length, 50.5 cm.; weight, 2,600 grams. The head showed extensive craniotabes, involving symmetrically almost all of the upper and posterior part of the parietal bones and the anterior portion of the occipital bones. There was slight but definite enlargement of the epiphyses of the wrists. The lungs were clear. A loud blowing systolic murmur (due to a patent intraventricular septum) was heard over the whole precordium, and was transmitted to the axilla and back. The spleen was felt. There was no evidence of infection. The diagnosis was: rickets, and congenital malformation of the heart.

The roentgenograms of the radius, ulna, tibia and fibula taken, July 17, when the baby was only 34 days old, revealed marked rickets (Fig. 1). The lower ends of both radius and ulna were abnormally broad and cupped. They did not end sharply, but had a frayed appearance. The shafts cast a less dense shadow than that caused by normally calcified bone. The tibia and fibula showed similar changes. At that time, the calcium of the blood was 9.0 mg. per hundred cubic centimeters of serum; the inorganic phosphorus, 2.2 mg. per hundred cubic centimeters of serum. There was a moderate secondary anemia, with hemoglobin 50 per cent. and 4,408,000 red blood cells. The blood Wassermann reaction was negative. The tuberculin test (0.02 mg., intradermally) was negative. The urine examination was negative.

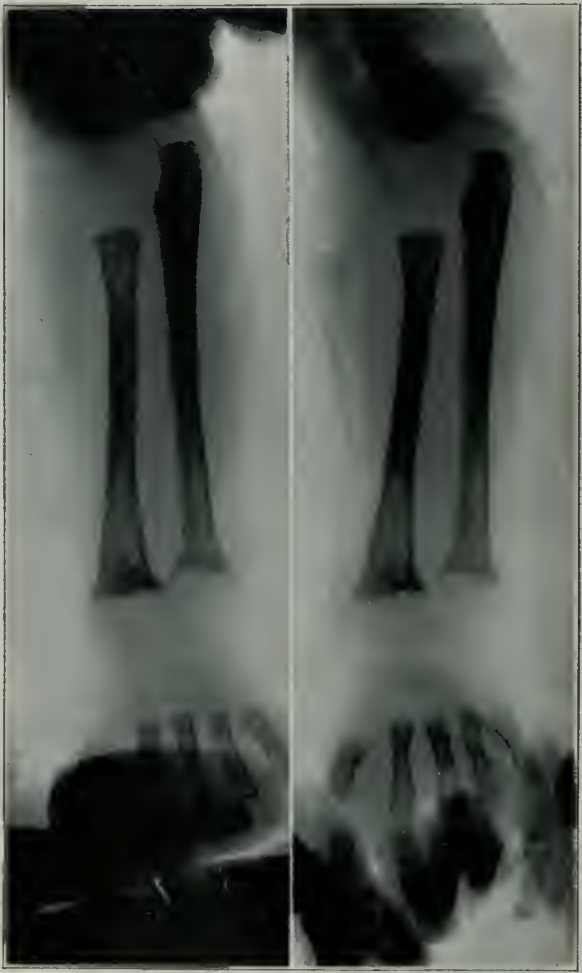

Fig. 1.—Radius and ulna. The flaring of the lower ends of the bones, the irregular frayed appearance, lack of calcium deposition and rarified appearance of the bone are evident.

Outcome.—The baby did not thrive. August 14, the temperature rose abruptly, and signs of pneumonia developed. August 15, at the age of 2 months, the infant died.

Necropsy Findings.—Rickets, congenital malformation of the heart and terminal bronchopneumonia were found. The thorax showed typical deformities.

The costochondral junctions were greatly enlarged on the inner surfaces and were slightly enlarged externally. Twenty-four fractures of the ribs were counted, and doubtless many more were actually present (Fig. 2). They were green-stick fractures and were marked by callus formations which formed distinct enlargements on the inner surface of the thorax. The ends of the radius and ulna and tibia and fibula showed characteristic enlargements. The bones offered little resistance to cutting. The slices taken longitudinally through the the cartilage-shaft junctions showed the typical rachitic intermediate zone or metaphysis.

Histologic Examination.—On microscopic examination of the lower end of the radius (Figs. 3 and 4), the proliferative zone of cartilage was considerably deeper than normal and sent numerous irregularly shaped prolongations toward the shaft. The cartilage cells composing the prolongations were for the most part in the same stage of development as those found normally in the proliferative zone close to the shaft. At the borders of the prolongations, however, in close proximity to the blood vessels of the marrow, the cells had lost their staining properties, and they and their matrix were undergoing transformation into osteoid.

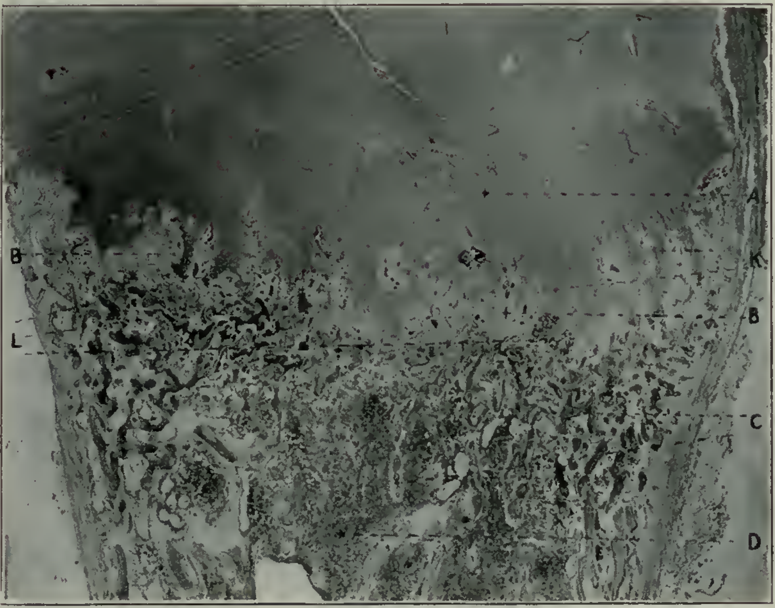

Fig. 2.—Low power view (magnification × 9) of the lower end of the radius of M. G., at age of 2 months. The irregularity of the junction of the cartilage with the shaft is characterized by an intermingling of prolongations from the cartilage (*k*) and prolongations from the shaft (*b*). Depositions of lime salts can be seen near the terminations of some of the prolongations of the cartilage (*l*). The proliferative zone of cartilage is much wider than normal. The trabeculae (*c*) are readily seen, and the osteoid borders easily recognizable. The marrow (*d*) seems fairly normal. The marrow does not fill in all the interspaces between the trabeculae. The trabeculae are surrounded by investments of fibrous tissue, which for the most part exclude the marrow from the spaces between them.

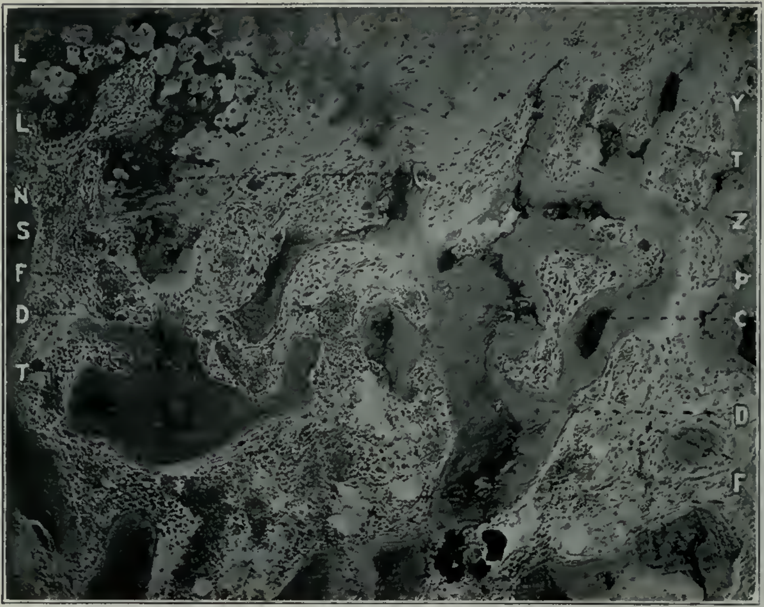

Fig. 3.—High power view (magnification × 70) of the lower end of the radius. At *z* can be seen the end of one of the prolongations of cartilage extending from the proliferative zone to the shaft through the rachitic metaphysis or transitional zone. The peripheral portion of this prolongation of cartilage has lost its normal staining reaction to hematoxylin and is undergoing transformation into osteoid (*y*). The cartilage cells are taking on the characteristics of osteoblasts. At *l* can be seen dense deposits of lime salts, appearing as irregular black areas. The characteristic changes in the trabeculae are well shown. In their central portions, the trabeculae are calcified, but in the peripheral portions they are free from lime salt deposits, and appear light pink in the preparations stained with eosin and hematoxylin. The trabeculae present, therefore, the osteoid borders characteristic of rickets. In the osteoid, the bone corpuscles can be plainly seen. The investments of fibrous tissue (*f*) about the trabeculae are also visible. The fibrous tissue lies next the trabeculae, and separates the marrow (*d*) from the trabeculae. The destruction of the trabeculae is proceeding apace. At *p*, the calcified central portion of the trabecula is being destroyed. In many parts of the sections, there seems to be a selective destruction of the calcified portions of the trabeculae rather than of the uncalcified portions by the blood vessels with their investments of cells (the perforating canals of the German pathologists). At *t*, the osteoid borders of the trabeculae have been destroyed, and the central cores have been exposed, eroded and in large part destroyed. The same has occurred at *s*. Where destruction of the lateral portions of the trabeculae is taking place, osteoclasts (*n*) are numerous. Osteoclasts also are found in niches or cavities at the edges of the trabeculae. In general, the osteoclasts lie against or close to a calcified portion of the trabecula, but some of them seem to lie in contact with the uncalcified portions. The evidences of the destruction of the trabeculae are almost as marked in the bones of M. G. as in the bones of rachitic rats on diets deficient in calcium.

At certain points, particularly where pressure was being exerted, the cartilage cells seemed to be reverting to earlier stages of development. At the ends of some of the prolongations were heavy deposits of lime salts. The prolongations of cartilage were separated from each other by prolongations in the opposite direction from the marrow. The latter were composed of blood vessels, some of which terminated close to the cartilage cells in bulbous enlargements. An enveloping loose connective tissue was also present. This connective tissue had a gray appearance in the hematoxylin and eosin stained specimens, and consisted of long thin connective tissue cells having rod-shaped nuclei (the "fibrous marrow" of the German authors). The prolongations from the marrow, interdigitating with the prolongation from the cartilage, together formed the rachitic metaphysis.

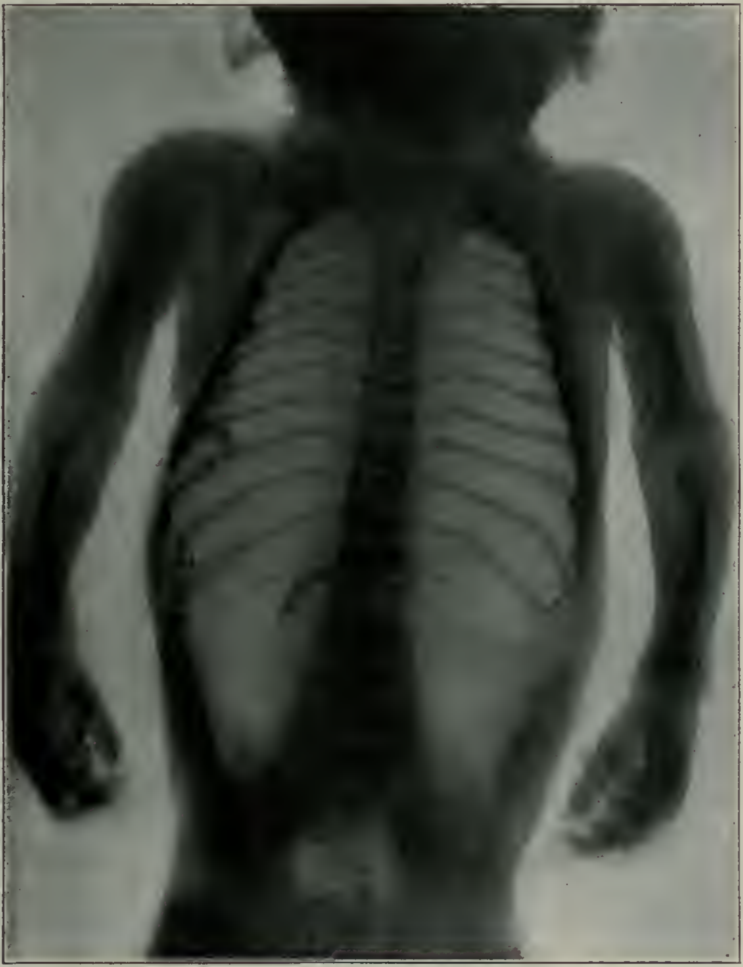

Fig. 4.—Thorax and upper extremities of patient after viscera had been removed. Numerous fractures of the ribs and marked flaring of lower ends of long bones, with cupping, are evident; also the absence of normal density in the cartilaginous zone.

At different points in the metaphysis, there were small masses of cartilage cells which, in the sections, seemed to be completely cut off from the main mass of cartilage. These were undergoing change into osteoid. The trabeculae of bone were calcified centrally. Their margins, however, were free from lime salt deposition, and formed the typical osteoid borders which are characteristic of rickets. The trabeculae were surrounded by thick investments of the connective tissue already described. Evidences of the destruction of trabeculae were found everywhere.

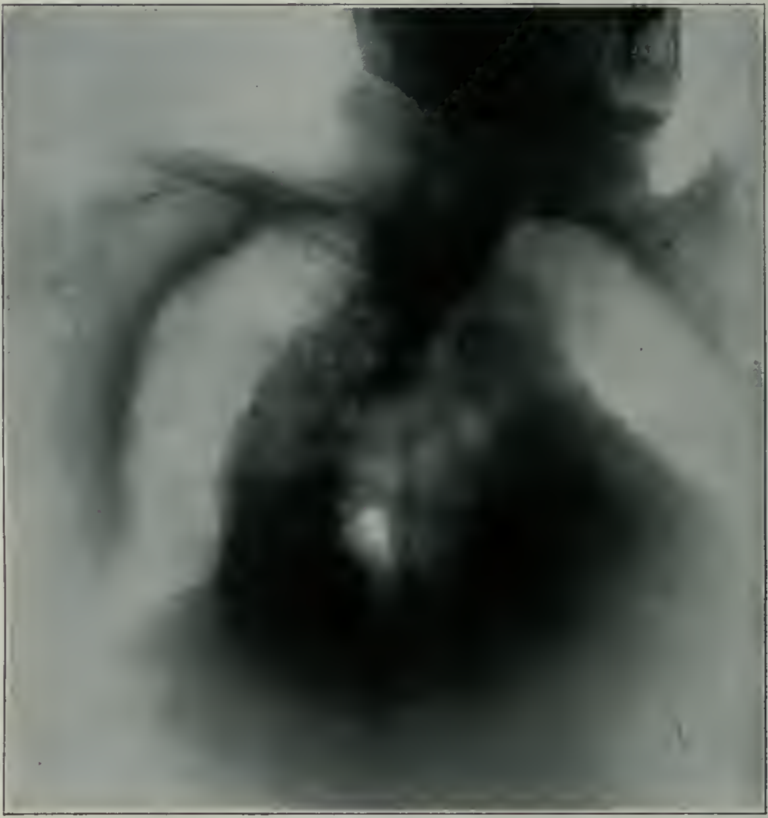

Fig. 5.—Thorax of Mrs. G., mother of patient. The roentgenogram reveals marked scoliosis and rarefaction of clavicles and scapulae. It is not sufficiently good to permit positive diagnosis of osteomalacia, but strongly suggests that condition.

In some places, blood vessels surrounded by investments of cells seemed to have bored into the calcified and also the uncalcified portions of the trabeculae, destroying them. In other places, the osteoid sides of the trabeculae had been destroyed, and the calcified portions were exposed and evidently undergoing erosion. In such places, osteoclasts were invariably found. Osteoclasts, whatever their function, were exceedingly numerous at the margins of the trabeculae. They either lay along the eroded sides or in holes or small hollows at the sides or tips.

COMMENT

This case, then, was one in which rickets was already well developed at the age of 34 days. Craniotabes was so marked that from it alone the diagnosis could be made. Roentgenograms of the wrists and ankles revealed indisputable evidences of advanced rickets. The blood at that time showed a normal calcium, but a low inorganic phosphorus. It is thought that 34 days is the earliest age at which rickets has ever been proved to be present.

MALIGNANT EPITHELIAL THYMOMA

REPORT OF A CASE, WITH NECROPSY *

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AND
HELEN HARRINGTON, M.D.
CINCINNATI

Cases of malignant thymoma are rare. Rubaschow[1] compiled a list of thymic tumors described prior to 1911, including a series collected by Hoffman in 1896, which totaled fifty-two sarcomas, twelve carcinomas and ten tumors of various other types. Since then, barely a dozen had been reported, when one of us (Foot[2]) described a case in 1920; and only four reports are subsequently listed in the *Quarterly Cumulative Index* of the American Medical Association to date.

As the histology of malignant thymoma was presented and discussed fully in the 1920 article just referred to,[2] we shall limit ourselves to a summary of Ewing's excellent article on these tumors in his textbook on neoplastic diseases,[3] and to a brief review of an article by Symmers and Vance,[4] which has an important bearing on our case.

MALIGNANT NEOPLASMS OF THE THYMUS

There are three types of malignant neoplasm of the thymus: (1) lymphosarcoma; (2) carcinoma, and (3) spindle cell or myxosarcoma, which is very rare and whose exact origin is undetermined. Ewing believes it to be the same as that of the other types, the thymic reticulum.

1. Lymphosarcomas occur in the anterior mediastinum in young persons, surrounding and compressing the trachea, bronchi, pericardium and great vessels. They cause death by compression asphyxia and venous obstruction, which may come on gradually or suddenly. The more rapidly growing tumors are soft; but, as a rule, thymomas show a firm, nodular consistence, owing to fibrosis. The soft tumors may be very vascular and hemorrhagic. Rarely, one encounters cyst formation or softening. They may exhibit a lemon or creamy yellow

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* Received for publication, June 12, 1923.

[1] Rubaschow, S.: Virchows Arch. f. path. Anat. **206**:141, 1911.

[2] Foot, N. C.: Report of Case of Malignant Thymoma with Necropsy, Am. J. Dis. Child. **20**:1 (July) 1920.

[3] Ewing, James: Neoplastic Diseases, Ed. 2, Philadelphia, W. B. Saunders Co., 1922, pp. 912-923.

[4] Symmers, Douglas, and Vance, B. M.: Epitheliomas of Thymic Origin, Arch. Int. Med. **28**:239 (Sept.) 1921.

color. A strict encapsulation within the mediastinum has been a notable feature, but the more malignant tumors regularly adhere to the surrounding organs. The bronchial, cervical and axillary nodes have been invaded occasionally; but direct extension into the pleura and pericardium is rather characteristic, the hilum of the lung often remaining comparatively free. While most of these tumors are rather sharply limited to the thorax, metastasis to distant organs, such as the spleen, liver, pancreas, suprarenals, and kidneys have been observed. Perforation of the chest wall may take place.

The microscopic structure varies. In one group, it resembles that of Hodgkin's granuloma. Large cells appear and displace the lymphocytes, giving rise to a picture that resembles that of carcinoma. Sometimes, the tumors may be composed exclusively of small cells, but "the existence of a pure lymphocytoma of the thymus, apart from leukemia, does not seem to have been established." Ewing believes that the tumor cells are not lymphocytes, for they differ materially from these in their structure. Lymphocytes are scanty. The chief cell showing active growth and mitosis is often polyhedral, with an acidophil cytoplasm, vesicular nucleus and well-developed nucleoli. Abortive Hassal's corpuscles may be produced.

2. Thymic carcinoma occurs in elderly persons; shows less tendency to metastasize than do most carcinomas, and is composed of sheets or columns of large, flat or polyhedral cells, with a dense connective tissue stroma. No cornification takes place, but structures resembling Hassal's corpuscles may be found. Ewing believes that this type of thymoma may be connected in some way with a perversion of the involution of the gland. Our case, occurring in a child of 2 years, would indicate that this is not necessarily true.

3. Thymic sarcomas of a spindle cell type have been described, and their origin attributed to the stroma of the gland. Myxosarcomas in which myxomatous tissue contained lymphocytes and Hassal's corpuscles have been reported.

Ewing strongly inclines to the view that the thymomas may be of infectious origin, a theory analogous to that held by many in connection with Hodgkin's granuloma. Having reviewed the material of one of Symmer's cases, which is indistinguishable from a thymoma, he believes that many cases described as Hodgkin's granuloma of the mediastinum are, in reality, thymomas; and he thinks that the two processes may be of an inflammatory, rather than a neoplastic, origin. It would seem, however, that there is no better actual proof that this is so than there is that the contrary is true; both thymoma and Hodgkin's granuloma may be placed just as readily in the category of neoplasms, with a brisk reaction on the part of the stroma and evidence of chronic inflammation due to the presence of tumor cells.

In reporting a case of epithelioma of thymic origin, Symmers and Vance [4] outline the types and groups of thymic tumors much as does Ewing, but they add that the term "thymoma," as applied to the lymphoid tumors, is permissible, if at all, only when used to denote a tumor that reproduces the structure of the thymus as a whole, including lymphocytes, epithelial reticulum cells and Hassal's bodies. They state that but four examples of true primary epithelioma of this organ are to be found in the literature, including theirs. One case each was reported by Paviot and Gerest,[5] Thiroloix and Debre,[6] and Rubaschow.[1] We shall return to a discussion of Symmers' and Vance's paper later, when comparing our case with theirs. In concluding, these authors state that the lymphocytic tumors are much more numerous than the epithelial and occur in persons under 35 years of age, many of them in children; while the four recorded cases of epithelial type have occurred in persons over 50.

REPORT OF CASE

History.—A girl, aged 2 years, colored, admitted to the Cincinnati General Hospital, March 5, 1923, having been brought in by her foster-mother, with whom she had lived for over a year and by whom the meager history was given, was thought to have enlarged tonsils, and this was the chief complaint. Her father and mother, who had six children, were alive and well, as were four of the children. The other child had died of a cause undetermined.

Prior to the time the patient came to live with her foster-mother, her history was unknown. She had never been well since coming under this woman's observation, having constant "trouble with her throat," difficulty in swallowing and paroxysms of coughing and strangling while attempting to drink, but apparently no pain. She would "pick at her throat," particularly at night, and her symptoms were subject to variations in intensity. She had no dyspnea, except when she had a paroxysm of coughing. She had fever at times, when the coughing was at its worst, and her foster-mother attributed it to tonsillitis. Although she frequently gagged, she did not vomit; her appetite was good, and she gained steadily on a diet of milk and potatoes, although she was very constipated. She had no important urinary symptoms.

Physical Examination.—At the time of admission, it was noted that respiration was slightly exaggerated, the alae nasi moving with each breath. The child was mentally alert and apparently not in pain, but she pulled constantly at her throat with her hands. The tonsils were very large, and the cervical, axillary and inguinal lymph nodes were palpable. No pharyngeal abnormality could be determined on digital examination. The patient was not cyanotic. The chest was well developed. The lungs showed normal resonance throughout the right side, but resonance was impaired over the left apex anteriorly and posteriorly, and was higher-pitched over most of the left side of the chest. The breath sounds were close to the ear and harsh over the right chest, and somewhat prolonged over the apex. In the left side of the chest, these sounds were somewhat suppressed throughout, but this condition was most marked at the apex, where prolonged expiration was best heard. There were a few râles in the left apex, but no adventitious sounds were heard elsewhere.

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[5] Paviot, J., and Gerest: Arch. de méd. expér. et d'anat. path. **8**:699, 1896.

[6] Thiroloix, J., and Debre, R.: Arch. de méd. expér. et d'anat. path. **19**:668, 1907.

The right border of the heart was apparently normal, but the left was difficult to determine on account of the impaired resonance on that side of the thorax. The heart sounds were loud and clear at the apex and comparatively clear elsewhere. There was a loud systolic murmur heard everywhere over the left side, but most marked in the second interspace in the nipple line. The abdomen projected above the level of the thorax. There was no palpable rigidity or masses. The liver and spleen were not felt. The patient winced on deep palpation. The reflexes were all normal.

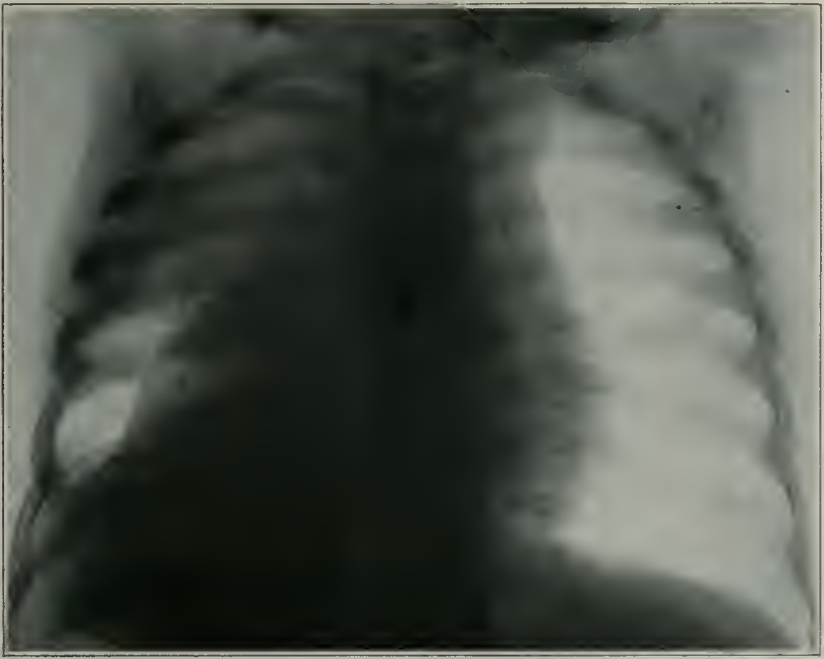

Fig. 1.—The striking similarity of the densest shadow on left to enlarged heart is evident (taken, March 10).

Summary: The principal findings on examination were: 1. Constant clutching at throat. 2. Large tonsils. 3. Impaired percussion note over left side of chest, with most marked impairment at apex. 4. Roughened voice sounds and diminished breath sounds over left side of chest. 5. Systolic cardiac murmur heard everywhere over left side of chest, but best in second left interspace.

Admission diagnoses: (1) Hypertrophic tonsils and (2) unresolved pneumonia in the left apex were diagnosed.

Course in Hospital.—March 6: The larynx was examined, but nothing abnormal was detected. Fluoroscopic examination of the esophagus after the ingestion of a barium sulphate meal failed to demonstrate anything of a pathologic nature.

March 10: Roentgenograms revealed a marked increase in all diameters of the heart, suggesting congenital enlargement. There was also a definite haziness over the left apex, suggesting infiltration. The fact that the diaphragmatic shadow was very high on the left pointed to some subdiaphragmatic pathologic condition (Fig. 1).

March 21: The patient's temperature rose to 102 F. and she coughed frequently. The chest signs were little changed.

March 28: Fluoroscopic examination revealed an area of density in the upper left lobe, extending almost to the base. The diaphragm was still high and fixed, being apparently held by adhesions. Two unsuccessful attempts were made to aspirate the left side of the chest.

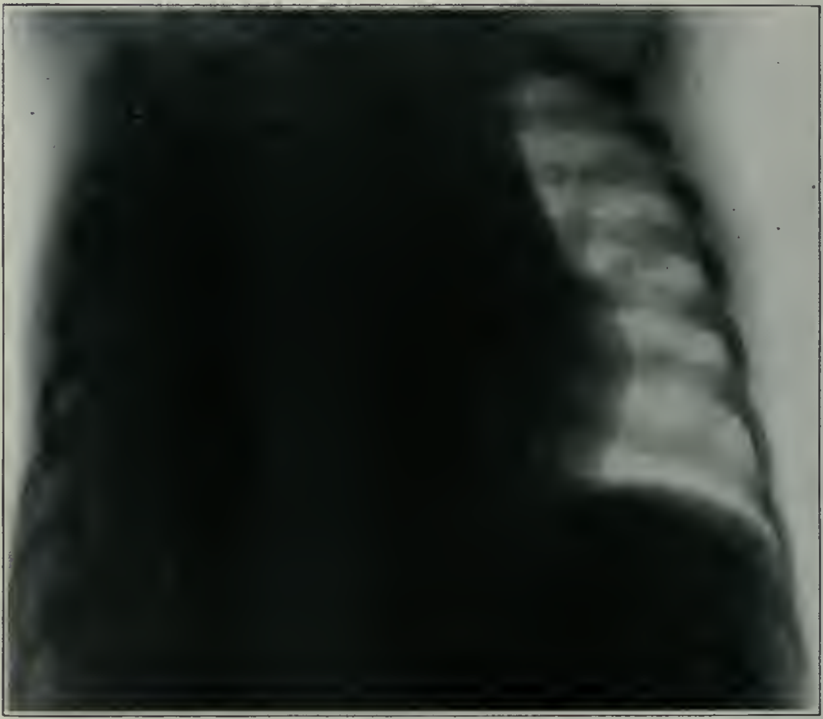

Fig. 2.—Complete obliteration of left side of chest by large shadow is shown (taken, April 3).

March 29: She lost her appetite and had difficulty in swallowing. She suffered also from attacks of dyspnea. The percussion note was now markedly impaired over the entire left chest, except anteriorly at the base. The breath sounds were distant and tubular on this side, and harsh, with occasional coarse crackles or wheezes over the right.

March 31: Signs of fluid in the left chest, confirmed by roentgen ray, were so marked that aspiration was again carried out, about 50 c.c. of fluid being removed. This at first appeared to be pure blood, but on centrifugation showed but two parts of red cells to ten parts of fluid, and a lower red count than normal for blood. Stained smears showed no abnormal cells, and cultures were sterile. The presence of bloody fluid at this time was thought to be the result of the trauma incidental to the first aspiration. No pathologic cells were found, such as might indicate the presence of a tumor.

April 9: The heart was displaced to the right; signs of fluid were still present, and aspiration resulted in the withdrawal of 50 c.c. of straw-colored fluid, in which no tumor cells were found.

April 21: Roentgenograms revealed the density already referred to persisting over the entire left chest. Plates taken between March 12 and April 21 showed merely a progressive increase in this density and in its extent (Fig. 2).

April 26: Signs of fluid in the left side of the chest again became more marked, and 125 c.c. of dark, bloody fluid was removed. It was now felt that the presence of blood could not be accounted for on the basis of trauma alone. The presence of a new growth, affecting the pleura, was considered probable, although roentgenographic examination revealed no masses, and no tumor cells had been found in the fluid previously. That obtained at this time was lost through accident and no examination could be made.

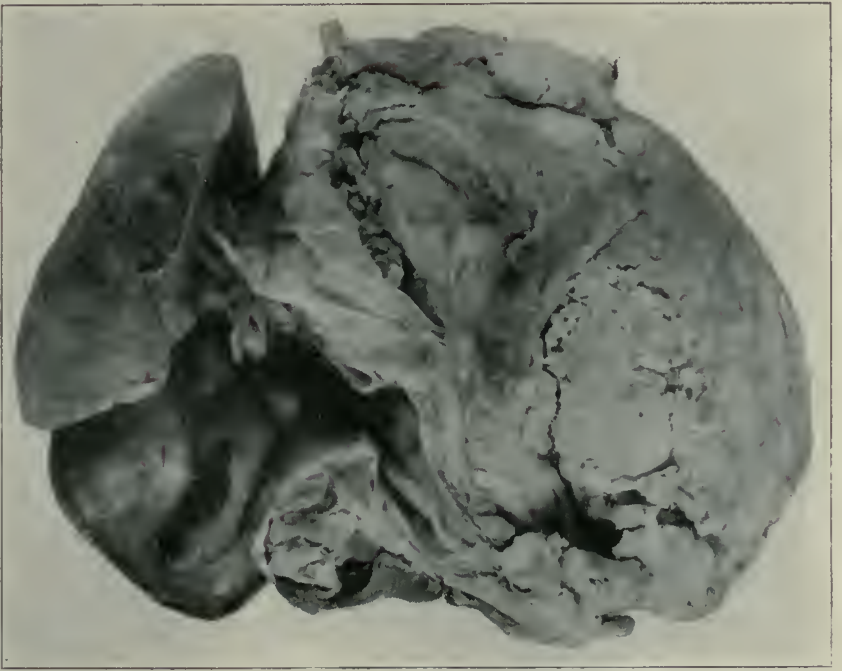

Fig. 3.—Anterior view of tumor and right lung. The heart has been removed from the dark recess at left center. The compressed thymus is visible at upper center to left of prominent nodule.

April 29: Aspiration was again attempted, with the hope of securing enough fluid for sections of a clot, but only 2 or 3 c.c. was obtained. Smears showed no abnormal cells and cultures were sterile. The patient gradually became weaker and more apathetic, the cough and dyspnea increasing

May 10: Respiration became very rapid, and the patient would lie only on the left side. No breath sound could be heard on the left and they became diminished on the right. The percussion note was hyperresonant over the right side, except at the base, where there was some impairment. The heart was rapid It was displaced to the right, and its sounds were very weak. In the evening, the child died suddenly of cardiac failure and pulmonary edema.

Laboratory Findings.—Urine examination, throat cultures, vaginal smears, tuberculin and Wassermann tests and all cultures from the pleural fluid were negative.

Blood examination (March 5) revealed: white blood count, 17,600; polymorphonuclears, 32 per cent.; eosinophils, 1 per cent.; lymphocytes, 65 per cent.; large mononuclears and transitionals, 2 per cent.; (March 30): white blood count, 14,600; polymorphonuclears, 61 per cent.; lymphocytes, 36 per cent.; large mononuclears and transitionals, 3 per cent; (April 28): white blood count, 20,000; polymorphonuclears, 60 per cent.; lymphocytes, 34 per cent.; large mononuclears and transitionals, 6 per cent.; red blood count, 3,860,000; hemoglobin, 45 per cent.

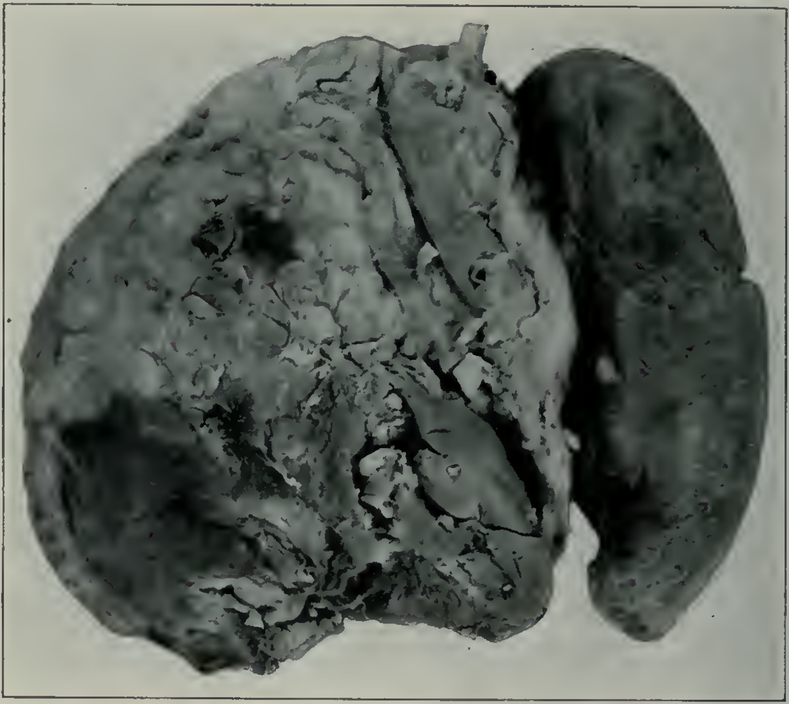

Fig. 4.—Posterior view of tumor and right lung, with remnants of left lung below. Small metastasis on inner, posterior surface of right lung is to be noted, and photograph compared with Figure 1.

Necropsy Findings (April 30, fourteen hours postmortem).—The body was well developed and well nourished. Rigor mortis was complete in the extremities and lower jaw. There was nothing abnormal to be noted externally. No discharge was found at the external openings of the various tracts. The pupils were equal, and 4 mm. in diameter. The intraocular tension was very low.

Primary incision: This was limited to the chest by the restrictions of the permit. It extended from the suprasternal notch to a point a little below the ensiform cartilage, exposing a moderate layer of fat. The thorax was found to be wide and deep. The diaphragm was flush with the lower costal margin on the left and definitely flattened out. On the right, it was at the seventh rib and normally dome shaped. This is interesting in view of the roentgen-ray findings, which indicated an abnormally high position of this organ on the left. On removal of the sternum, several cubic centimeters of a straw-colored fluid, with whitish-yellow masses of soft, puriform material floating in it, escaped, and a tumor mass presented over almost all of the region exposed.

The new growth was intimately adherent to the chest wall on the left and had forced the left lung downward and backward, compressing it until it was a mere mass of flabby, fleshy material. The heart was displaced to the right until its long axis lay almost in the midline, approximately vertical, the apex pointing slightly to the right. The right lung lay free in its pleural sac and was invaded but slightly by the tumor. As the latter is the most important structure encountered, it will be described first.

The tumor: This was roughly globular in shape, as can be seen from figures 3 and 4. It measured 10 cm. in its vertical, 9 cm. in its transverse and 8 cm. in its anteroposterior diameter. Its color was yellowish white; its surface coarsely nodular, and its consistence varied from firm to almost pultaceous. The thymus overlay the growth above and in front, forming a pinkish layer about 5 mm. thick, definitely separated from the yellowish mass of new growth behind and beneath it. Here and there nodules of the tumor penetrated to the anterior surface, forcing the thymic tissue aside.

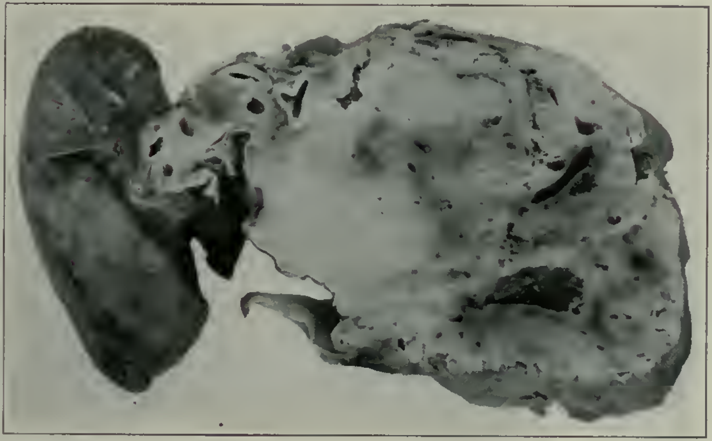

Fig. 5.—Transverse section of tumor at level of hilum. The esophagus, three bronchi and the pulmonary vessels will afford orientation.

The tumor, lungs and heart were removed in toto and in continuity. It was found that the first was composed of coarse nodules, averaging about 2 cm. in diameter in its upper part, and more homogeneous in its lower or main portion. The left parietal pleura was invaded extensively by infiltrating masses of soft pulpy tumor tissue, which tore away from the main growth when it was removed from the body.

Heart: This was removed from the pericardium, and it was found that the latter was quite free from any gross evidence of tumor infiltration and contained a small quantity of straw-colored fluid. The heart weighed 50 gm., and presented nothing at all abnormal.

Lungs: The right lung was preserved in continuity with the specimen, so that its weight cannot be given. It was slightly congested and moderately emphysematous, and presented two tumor metastases on its diaphragmatic surface; one of these was discoid, 2 cm. in diameter, and about 5 mm. thick, obviously situated in the pleura. The other was larger, 1.5 cm. square, and pyramidal in shape, penetrating the lung tissue to a depth of 3 cm. or more, its apex directed toward the hilum. A third metastasis, shown in Figure 4, lay in the pleura near the hilum and slightly behind it. This was also discoid, 1 by 1 by 0.5 cm. in size. Otherwise, the organ was normal in appearance, the pleura smooth and shining and no other masses palpable. It is important to note that the hilum shows no enlargement of its lymph nodes. It was quite freely movable and normal on palpation.

The left lung was compressed until it was a mass of fleshy tissue and quite airless. Figure 5, showing a section through the hila of both lungs, reveals how the tumor had invaded and replaced this organ by spreading downward along the inner aspect of the pleural lung capsule. It will also show the involvement of the esophagus, bronchi and pulmonary vessels at this level. Exploratory lung sections revealed moderately numerous areas resembling foci of lobular pneumonia, as microscopic examination proved them to be. Gross examination did not indicate whether or not they were tumor or inflammatory infiltrates, but it was thought that they were the former. The hilum of the lung was embedded, as shown in Figure 5, in dense masses of the tumor. It is to be noted that these metastases in the lung were all in the immediate vicinity of the primary growth and usually spread by infiltration rather than by true metastasis, a characteristic of this tumor.

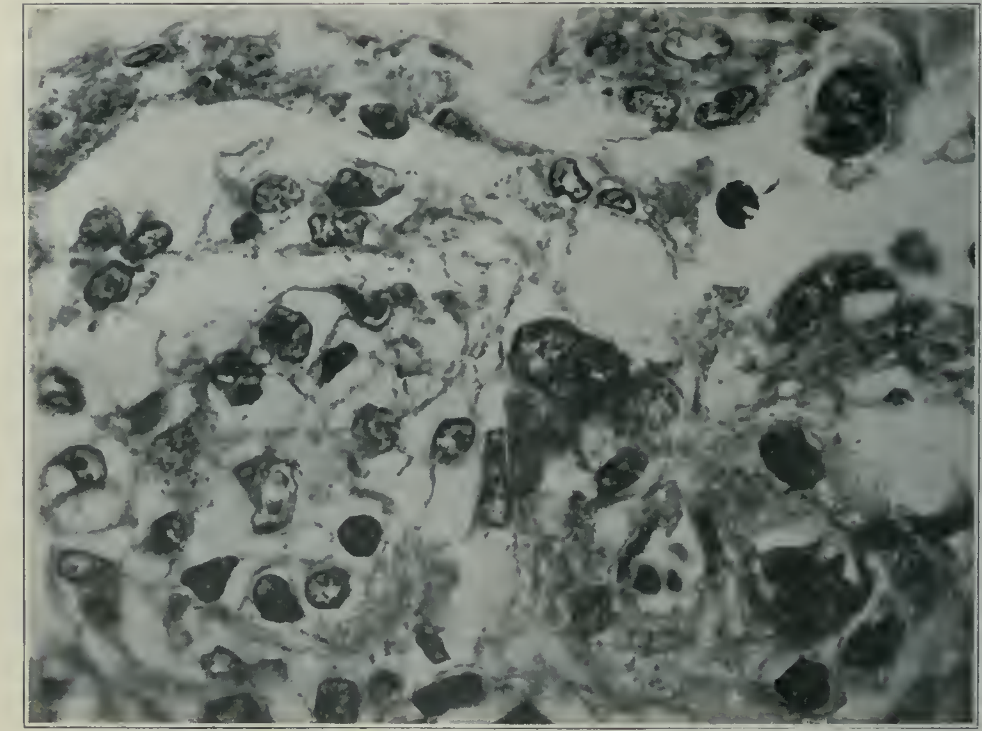

Fig. 6.—Photomicrographs of reticuloid type of growth, with rudimentary Hassal's corpuscle at right lower corner; × 650; hematoxylin-eosin stain.

Abdominal organs: The abdominal organs were removed by cutting away the diaphragm peripherally and severing the mesentery and rectum. It was noted that the liver was much enlarged, reddened and extended to the umbilicus. The spleen weighed 35 gm. It was almost as hard as stone, and its external surface was smooth and shining. On section, the parenchyma was found to be a deep purplish red, resembling porphyry. The pulp did not strip on the knife blade, and the malphighian corpuscles were indistinct; the trabeculae, vague. The picture was similar to that of cyanotic induration. The liver weighed 420 gm. Externally it was smooth and shining and rather pale brownish yellow. On section, much blood escaped from the widely dilated hepatic veins, which sometimes attained a diameter of 75 mm. or more. The markings of the organ were indistinct, despite the passive congestion. The parenchyma was pale yellowish brown, and shining. The organ diminished in size after the blood was allowed to escape. The gallbladder contained a small quantity of brownish bile, readily expressible through the papilla of Vater. The gastro-intestinal tract presented nothing of note. The suprarenal glands were intensely congested in their medullary portions, blood escaping under pressure, on section. The mesenteric nodes were universally enlarged, some measuring as much as 2 cm. in long diameter. They were somewhat congested. The pancreas was not remarkable, nor were the kidneys.

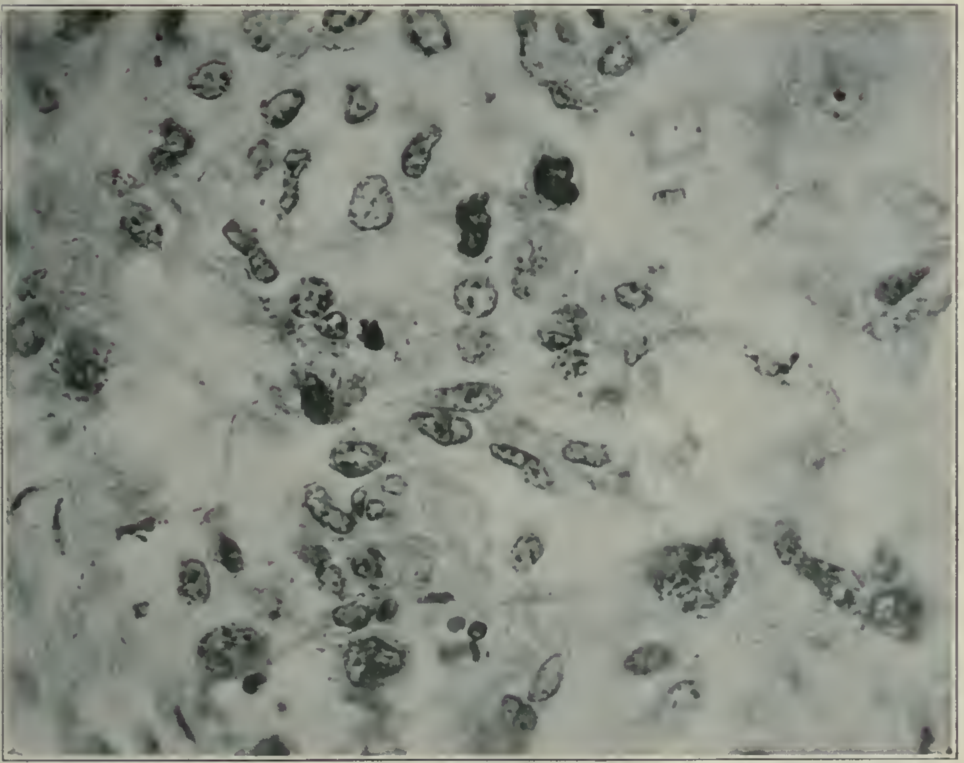

Fig. 7.—Photomicrograph of reticuloid type of growth; × 650; phosphotungstic acid hematoxylin stain.

The anatomic diagnosis was malignant thymoma of the anterior mediastinum, involving the left lung and, to a far lesser extent, the right; chronic passive congestion of the liver, spleen and suprarenal capsule, and chronic hyperplasia of the mesenteric lymph nodes.

Microscopic Examination.—The tumor was composed of cells which showed three definite types of growth: (1) a reticuloid, resembling the embryonic thymic reticulum; (2) an epithelioid, resembling an adenocarcinoma or a medullary carcinoma; and (3) a sarcomatoid, resembling a large, round cell lymphosarcoma or fibrosarcoma.

1. The reticuloid type. This was found in most of the sections examined and constituted the more typical pictures of the tumor. Sections from areas showing this form of growth showed a striking resemblance to Hammar's illustration of the thymic reticulum in a 70 mm. embryo, as pictured in Ewing's textbook[3] (page 913). The cells were polyhedral, with a large, often lobulated, ovoid, vesicular nucleus, coarse and distinct nuclear network, and one or more distinct nucleoli, which stained pinkish with eosin. The cytoplasm was delicate and branching, the cells anastomosing freely with one another to form a delicate reticulum, which stained pink with eosin, red with acid fuchsin, and yellowish or reddish brown with phosphotungstic acid hematoxylin. Masses of reticulum formed innumerable alveolar structures in a meager connective tissue stroma. The average diameter of these cells was about 10 to 12 microns. Besides forming the reticulum, they frequently clumped together into masses which might be interpreted as immature Hassal's bodies, as they sometimes showed a slight tendency on the part of the cells to form concentric layers; but this was seldom

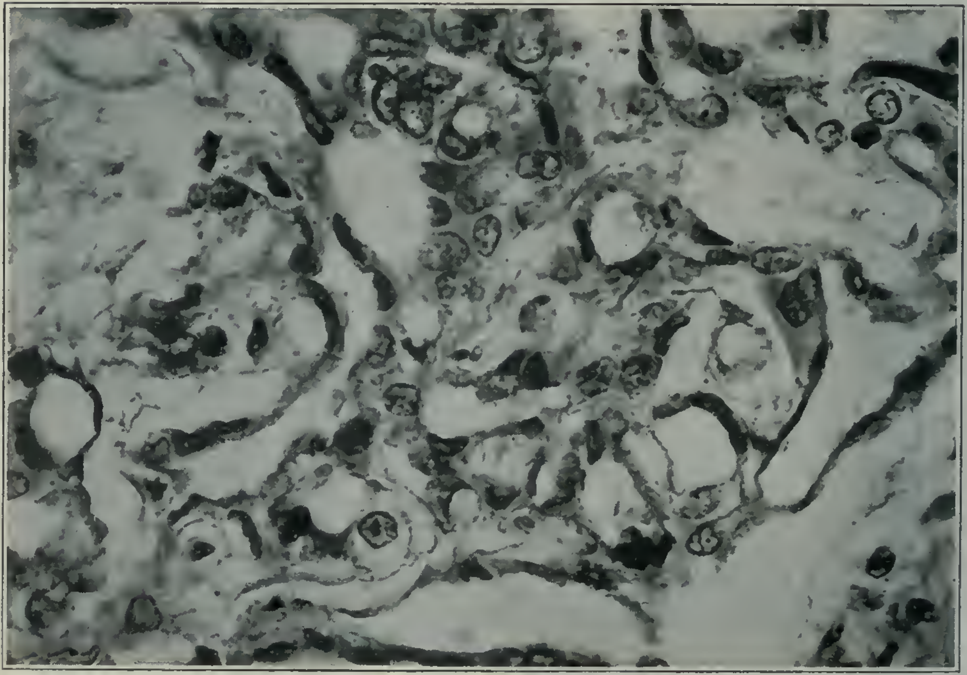

Fig. 8.—Epithelioid type of growth, ducts and reticulum; × 650; hematoxylin-eosin stain.

seen. Many tumor giant cells were found in this type of growth. Gigantic masses of lobulated nuclear material, or multiple nuclei occupied the greater part of the cell body, so that the cytoplasm was very inconspicuous. These cells measured from 18 to 20 microns. In Figures 6 and 7, two typical fields from the reticuloid portion of the tumor are shown. Figure 6 shows one of the masses of cells that might be interpreted as a very immature Hassal corpuscle.

2. The epithelioid type. This type of growth is shown in Figure 8. Here the cells were grouped into glandular complexes, which exhibited a tendency to form thin-walled and branching duct-like acini. Sometimes, the component cells were flat and elongated on section, sometimes cuboidal. In the former instance, they measured from 11 to 12 microns in length, and but 2 to 3 microns in thickness. In the latter, their diameter averaged about 8 microns. Their nuclei were spherical; stained deeply with nuclear dyes, and did not show the definite filamentous chromatic structure seen in the reticuloid variety. However, there were places where these ductlike structures faded imperceptibly into those of the reticular type, which often were associated with them. The stroma was made up largely of connective tissue, but parts of it were formed by the reticular tumor elements. No ciliated epithelium could be found in these ducts. Occasionally, a colloid secretion was encountered in connection with these, but it was present only in small quantities. In other parts of this type of growth, the cells, instead of forming ducts, were arranged in flat sheets, or masses, resembling those of a medullary carcinoma, without any tendency toward the formation of a reticulum.

3. The sarcomatoid form. This was met with in the pulmonary metastases, when the tumor had invaded the pleural connective tissue. Here, the cells were embedded discretely in dense, fibrous tissue, or lay in nests among its fibers, without anastomosing with one another. They were more or less spherical; averaged 8 microns in diameter, and possessed very little cytoplasm. They reminded one of some of the larger cells in the thymoma described by one of us,[2] resembling those of a lymphosarcoma that shows little maturity. The nuclei of these cells presented an appearance midway between that of the reticular cells and the epithelial duct cells, in that they were denser than those of the former, and less so than those of the latter. These portions of the tumor showed many enormous giant cells, often of very bizarre appearance and outline, which measured about 30 microns in length and from 18 to 20 microns in transverse diameter. Their nuclei were either lobulated or multiple, presenting groups of five or more. Another interesting feature about this type of growth was the presence of much fibrin in the form of thick fibrils that lay in groups between and about the cells, often forming a network, like small baskets. They always showed prominent nodal intersections and were best seen in the phosphotungstic acid hematoxylin sections.

Summary: In general, the tumor showed a great deal of necrosis, with a striking lack of vascularity, except where vessels already were present in the invaded tissue. In the necrotic areas, it was observed that the tumor formed halos of reticulum about the vessels, and that these zones faded off into the necrotic tissue on the one side and the vascular adventitia on the other, so that the effect was very misleading. If one had no other criteria for diagnosing the epiblastic character of the growth, one might have attributed an adventitial origin to this tissue. The tumor was evidently of extremely rapid growth, as mitotic figures were very abundant and present in all types of cells, the giant-cells presenting strange multiple mitoses in many instances.

Frozen sections stained with sudan III showed a large amount of sudanophil material, both in the cells of the stroma, where it appeared as coarse droplets, and in the cells of the ductlike and acinar structures. Nile blue sulphate showed this fatty material to be in part neutral fat, when present in coarse droplets, in part lipoid substances, when it was in the epithelium in the form of coarser or finer navy-blue granules. The presence of fats and lipoids in this tumor indicates nothing more than an extensive degenerative infiltration. The lipoids were found in the healthier, the neutral fat in the more degenerated or in the necrotic portions, of the tumor.

Thymus: This was found to have been compressed and flattened. Hassal's corpuscles were very numerous and close together. Many of them showed cornification and invasion by leukocytes, as in involution, but most of them were of an immature type, mere collections of reticulum cells. There was a definite increase in the amount of reticulum, which was hypertrophic and compact. The eosinophil cells were not present in large numbers, but cells of the lymphocytic type were there in the usual amount. At the margin of the gland, where it was separated from the tumor only by its capsule, there was sometimes a still more marked increase in the reticulum, with its cells packed closely together. The only other feature that needs discussion is the presence of prominent strands of hyaline material that appeared to be connected with Hassal's bodies and radiated from them. It was composed of compacted reticulum. No tumor cells were found in the thymic sections examined, and no gradual transition from normal thymus to thymoma was observable.

Other organs: Little was discovered in the examination of the heart, liver, kidney, pancreas and suprarenal gland. Despite the gross evidence of passive congestion, there was little to indicate it in the microscopic sections. The spleen, however, was intensely congested, and the malpighian corpuscles were compressed and inactive. The trabeculae and capsule were somewhat thickened. The lungs showed the presence of the tumor and of the lobular pneumonia described in the gross. There was a marked purulent bronchitis and moderate passive congestion, with compensatory emphysema in some sections.

COMMENT

The clinical and pathologic features of this case are interesting. From the clinical standpoint, its chief appeal is the difficulty it presented to diagnosis. Perhaps the most striking point is the fact that the roentgen-ray examinations were not only of no assistance, but also were actually misleading, owing to the asymmetry of the growth and its encroachment on the left side. Roentgenograms of thymomas usually reveal shadows in the midline, in the mediastinal region. (Compare those of Ewing and Foot.) In this case, the distribution of the growth, with the compression and destruction of the left lung, combined to produce a shadow that was indistinguishable in location and outline from that thrown by an enlarged heart. A comparison of the roentgenograms and the photographs of the specimen will show at a glance why this was so, and how readily one might be mistaken in interpreting the roentgenograms. The roentgen ray also failed to demonstrate any marked irregularity of the shadows which might be construed as indicating the presence of a tumor.

No tumor cells were found in the fluid aspirated from the chest, although repeatedly sought for; and, although a new growth was suspected, no positive proof of its existence was forthcoming. The compression of the aorta and trachea gave signs and symptoms. The former produced a loud systolic murmur that directed the clinicians' attention to the heart, which proved to be normal. The transient asphyxia and coughing caused by the latter was not enough evidence upon which to base a diagnosis of new growth. The blood counts and smears gave no assistance. It is strange that the compression of the esophagus by the tumor presented no difficulty to the passage of a stomach tube, which was readily introduced and withdrawn.

Pathology of the Tumor.—From the point of view of the pathologist, this tumor is of great interest. It is essentially epithelial in type, and it occurred in a baby, which alone stamps it as a rarity. The most important feature, however, is the light that it throws on the histogenesis of thymoma. Here, we have a tumor exhibiting a predominatingly reticular type of growth and substantiating Ewing's theory that thymomas not only arise from thymic reticulum, but may present a picture that is strikingly like normal embryonic thymus at an early stage of its development. Furthermore, the existence of glandular, or other definitely epithelial elements demonstrates the connection between this embryonal reticulum and the thymic carcinomas. That this ductlike growth represents remnants of the destroyed pulmonary tissue might be indicated; but the shading off of epithelium into reticulum, and the infiltrative and metaplastic character of the ducts would seem to render that hypothesis unlikely. The sarcomatoid portions of the growth need little discussion. They resemble the dissociated form of structure sometimes observed in carcinoma of the pancreas or cervix; but it is interesting to compare them with the so-called lymphosarcomas of the thymus, and note the striking resemblance.

That this tumor is epithelial is indicated by the following facts: 1. It resembles the reticulum of the thymus, which is ectodermal. 2. It forms definite glandular and alveolar masses of cells. 3. The production of cell complexes vaguely resembling Hassal's corpuscles also indicates ectodermal origin, although the structures produced are a very poor imitation of the finished corpuscles, and would scarcely serve as a means of identification if taken alone.

Of the four articles appearing since 1920,[7] only two were available, that of Symmers and Vance and that of Sweany. The latter is a short case report that describes a case of thymoma in conjunction with tuberculosis, and does not throw much additional light on the subject. Tuberculosis is so common that it might occur in conjunction with any tumor. If Symmers and Vance are correct (and we have no reason to doubt them), this is the fifth case of primary epithelial thymoma to be reported and the only one occurring in a child. Our reasons for believing it to be epithelial have been stated. We think that it is primary because: it occupied the region of the thymic center (anlage); spread by direct extension rather than by metastasis; limited its extension chiefly to the pleura, and did not invade the pulmonary alveoli so far as we could ascertain. Most important is the fact that it gave no evidence that it had originated from any other organ that could bequeath to it the morphology shown by its cellular elements, which resembled embryonic thymus more closely than anything else. Our tumor does not correspond very closely with those that have been reported in older persons, but there is no reason why it should, as malignant epithelial tumors occurring in childhood are notoriously different from those appearing in old age.

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[7] Cleland, J. B., and Beare, F. H.: M. J. Australia **1**:182 (Feb. 18) 1922. Harvier, P.: Bull. et mém. Soc. méd. de hôp. de Paris **45**:874 (March 18) 1921. Symmers, Douglas, and Vance, B. M.: Footnote 4. Sweany, H. C.: Primary Tumor of Thymus Associated with Tuberculosis, J. A. M. A. **80**:754 (March 17) 1923.

We have retained the term thymoma for the reason that it is descriptive, while the more usual term "carcinoma" is not. Although the origin of thymomas is ectodermal, possibly in all cases, and certainly so in that of the epithelial tumors, the term carcinoma is, we think, misleading in a tumor of this type, which approaches the embryoma so much more closely in its morphology and in its variability of cell types, although it could not be one. We believe that in calling this tumor a carcinoma, one fails to indicate the polymorphic tendencies of its component cells; just as we believe that the term lymphosarcoma should not be used in connection with the lymphocytoid type of malignant thymoma, until it is proved that it is indeed a neoplasm of the lymphatic system. We would suggest some such term as thymic epiblastoma as appropriate, brief and indicative of the origin and the embryonal character of the growth. It could be applied to the lymphocytoid tumors only when they were sufficiently unlike lymphosarcomas to warrant it, or as soon as the ectodermal origin of the small thymic cells has been determined beyond a doubt.

PRELIMINARY REPORT ON THE KOTTMANN REACTION IN CHILDREN

WITH A NOTE ON THE TREATMENT OF CHOREA WITH THYROID *

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Kottmann [1] first described his test for thyroid activity in 1920. He had previously studied the serum in pregnancy, and from this work assumed that certain physicochemical differences must be present in the serums of patients suffering from thyroid dysfunction. Petersen, who first investigated the test in this country, thus describes the process:

> Because of the peculiar relation of iodin to the glandular metabolism, he (Kottmann) began his experiments with colloidal iodin preparations, using silver iodid for this purpose because of its well known photosensitivity. In the test as developed by him, certain phenomena commonly observed in photography play a rôle. Thus, when silver nitrate is added to potassium iodid, silver iodid is formed. In the presence of a protective colloid, the growth of the particles is retarded, depending on the protective property of the colloid used. In the photographic plate, a gelatin preparation is used for this purpose, and the prepared film (silver iodid or bromid dispersed in gelatin) is permitted to ripen. During this process of ripening, the colloidal particles of the silver salt gradually become larger, and as they do so, they become more photosensitive than when in the original highly dispersed state. If we substitute serum for the gelatin, a similar reaction might be anticipated, the particles of silver iodid formed becoming larger or smaller according to the protective property of the serum. The greater the photosensitivity of the silver iodid, the poorer the protective property of the serum used, and presumably, therefore, the coarser the colloidal dispersion of the serum itself. The less photosensitive the silver iodid, the greater the protective power of the serum and presumably the greater the state of dispersion of the serum colloids themselves.

Kottmann himself found that, in cases of exophthalmic goiter, there was a definite, and, in severe cases, a marked, change in the reaction compared to that found in control cases. Petersen [2] and others in a series of 400 cases obtained markedly retarded reactions in sixty-five

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* From the Children's Medical Division of Bellevue Hospital.

1. Kottmann, K.: Colloidal Chemical Studies of Thyroid Gland Problems, Schweiz. med. Wchnschr. **30**:644 (July 22) 1920.

2. Petersen, W. F.; H'Doubler, F. T.; Levinson, S. A., and Laibe, J. E.: The Kottmann Reaction for Thyroid Activity, J. A. M. A. **78**:1022 (April 8) 1022; Studies in the Kottmann Reaction for Thyroid Activity, Arch. Int. Med. **30**:386 (Sept.) 1922.

of the seventy cases of hyperthyroidism, and in eleven cases under bromid medication, thus confirming Kottmann's observations in these conditions. In the serums of patients with acute infections, Petersen found normal reactions in all except one, which was slightly retarded, and several accelerated reactions which occurred in the more severe infections. From his observations in this series, Petersen considers that the Kottmann reaction yields a close index of thyroid function. Kottmann found accelerated reactions in cases of goiter, but Kay [3] felt that the test failed in cases of hypothyroidism, although it gave definite indication of hyperthyroid conditions. He found that it checked with the clinical findings and basal metabolism. Petersen also studied the test in experimental conditions, and concluded that alterations obtained in the reaction "need not be associated with thyroid dysfunction. The thyroid dysfunction alters cellular metabolism and this in turn alters the physical properties of the serum so that in cases of hyperthyroidism the serum is a better protective agent than normally. If the cellular metabolism is altered by other insults, serum alterations must also take place, and these will be reflected in the Kottmann reaction."

Since no references were found as to the Kottmann reaction in children, this investigation was undertaken in the children's medical division at Bellevue hospital under the direction of the department of diseases of children at Columbia University, in the hope of discovering a means of differentiating between the various types of endocrine disturbance in the early stages.

TECHNIC

To 1 c.c. of clear serum is added 0.25 c.c. of a 0.5 per cent. solution of potassium iodid and 0.3 c.c. of a 0.5 per cent solution of silver nitrate. The tube is rotated gently, and then exposed for five minutes to a 500 watt Mazda lamp at a distance of 25 cm. Then 0.5 c.c. of a 0.25 per cent. solution of hydrochinon is added, and the color changes are noted. The final color is a dark reddish brown. Although theoretically the developing should be done in a dark room, the use of diffused daylight apparently did not alter the results. Normally, the reaction is complete in about ten minutes, and a reaction which is complete in about five minutes is considered accelerated. The specimens of blood were all taken in the morning, either with the patient fasting or about four hours after the morning meal.

GROUPS

For purpose of comparison, the 106 cases in which the reaction was studied were arranged in five groups. Group 1, the controls, was composed of twenty-eight children who showed no evidence of thyroid disturbance or of infection. The second group comprised thirty-three cases of acute infection; Group 3 was composed of eleven cardiac cases, and Group 4 consisted of thirteen cases diagnosed clinically as endocrine disturbances, and six cases of idiocy. The cases of chorea were put in a group (Group 5) alone because of the interesting results obtained, and will be considered in detail. The patients ranged from a 3 weeks old infant with eczema to children of 12 years.

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[3] Kay, W. E.: A Study of One Hundred Cases Diagnosed as Hyperthyroidism, J. A. M. A. **79**:2149 (Dec. 23) 1922.

RESULTS

In Group 1 (Table 1), twenty-one of the twenty-eight reactions were normal. No particular explanation could be made for the two slightly accelerated and the two slightly retarded reactions, nor for one of the three which were markedly retarded. One of these three patients, an epileptic, had been given bromids for a severe convulsion several hours previously, and the other, an infant who was recovering from a severe pneumonia, had been given calcium chlorid for two weeks consecutively. This last observation is interesting because of the findings of Kottmann, Petersen and Merke[4] that bromids prolong the reaction, and of Petersen that the administration of iodids also retards the reaction although in less degree.

Table 1.—*Miscellaneous Conditions (Group 1)*

Diagnosis	Number of Cases	Slightly Accelerated	Accelerated	Normal	Slightly Retarded	Retarded
Epilepsy	2	1	..	..	..	1 (bromid)
Rickets	11	1	.	8	2	..
Spastic paraplegia	1	..	..	1	..	..
Convalescent; pneumonia	3	..	..	2	..	1 (calcium chlorid)
Foundling	1	..	..	..	..	1
Convalescent; tonsillitis	1	..	..	1	..	..
Contracture of hand	1	..	..	1	..	..
Talipes equinus	1	..	..	1	..	..
Fracture of arm	1	..	..	1	..	..
Club foot	1	..	..	1	..	..
Chlorosis	1	..	..	1	..	..
Mercury poisoning	1	..	..	1	..	..
Diet regulation	1	..	.	1	..	..
Eczema	1	..	..	1	..	..
Well child	1	..	..	1	..	..
Total	28	2	..	21	2	3

In Group 2, the acute infections (Table 2), it will be noted that only thirteen of the thirty-three reactions were normal. Of the accelerated reactions, eleven occurred in children with severe infections, three of whom died subsequently, and one, who suffered from septicemia, went through a long illness, and in fact has not yet recovered. No special reason was found for the two slightly retarded or two of the markedly retarded reactions. The child with encephalitis who gave a retarded reaction and who later died had been given sodium bromid for extreme restlessness. In his first paper, Petersen suggested that border line cases, such as those of tuberculosis would be a fruitful field of investigation in relation to the Kottmann reaction. Hence it is interesting to note that one of our two cases of pulmonary tuberculosis showed an accelerated reaction, and that the other was slightly accelerated.

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[4] Merke, F.: Schweiz. med. Wchnschr. **51**:200 (March 3) 1921 (referred to by Petersen).

Group 3 (Table 3), the endocrine and idiocy cases, is entirely too small to permit of conclusions. It was also unsatisfactory because most of the cases were sent to us from the outpatient department, and had not been under our own observation, so that we had no method of control. Also, most of them had been under treatment with various glandular preparations for varying lengths of time. Only ten of the nineteen children had normal Kottmann reactions. One, who had clinically a fairly definite case of hyperthyroidism, gave the characteristically retarded reaction, and the child with the enlarged thyroid who gave an accelerated reaction nearly fainted during the blood taking. The two cretins are also of interest. One, a boy of 6, who had been taking thyroid intermittently for several years, gave a slightly accelerated reaction. The other, an infant of 14 months in very poor physical

TABLE 2.—*Acute Infections (Group 2)*

Diagnosis	Number of Cases	Slightly Accelerated	Accelerated	Normal	Slightly Retarded	Retarded
Meningitis	3	..	..	2	1	..
Bronchopneumonia	2	..	2	..	..	..
Tuberculous meningitis	1	..	1	..	..	..
Pneumonia	5	1	1	3	..	..
Bronchitis	3	..	..	1	1	1
Tonsillitis	1	..	..	1	..	..
Acute rheumatic fever	1	..	1	..	..	..
Septicemia	1	..	1	..	..	..
Influenza	6	..	3	2	..	1
Encephalitis	5	..	2	2	..	1
Acute nephritis	3	1	..	2	..	..
Pulmonary tuberculosis	2	1	1	..	..	..
Total	33	3	12	13	2	3

TABLE 3.—*Endocrine and Idiocy Cases (Group 3)*

Diagnosis	Number of Cases	Slightly Accelerated	Accelerated	Normal	Slightly Retarded	Retarded
Hypopituitary	6	..	1	5	..	..
Thymus and microcephalus	1	..	..	1	..	..
Cretin	2	1	1	..	..	..
Hyperthyroid	2	1	..	..	..	1
Goiter	1	..	1	..	..	..
Dyspituitary	1	..	..	..	..	1
Idiots	6	1	1	4	..	..
Total	19	3	4	10	..	2

condition, at first gave an accelerated reaction; but later, after three weeks of thyroid therapy, followed by distinct clinical improvement, gave a normal reaction.

Group 4, the cardiac cases (Table 4), was rather interesting. The three patients who gave normal reactions were in fairly good general condition, and two were up and about the ward. In the remainder of the eleven cases, with one exception, although they were compensated, the patients were all pale and undernourished, as is usual in these cases while in the hospital. The child with the slightly retarded reaction had pericarditis with effusion at the time the blood was taken, and had been receiving morphin for some time. Incidentally, two of the children with accelerated reactions were noted as being "stupid" and having enlarged thyroids. How much this may have had to do with the results of the test, it is impossible to state.

TABLE 4.—*Groups 4 and 5*

Diagnosis	Number of Cases	Slightly Accelerated	Accelerated	Normal	Slightly Retarded	Retarded
Cardiac cases	11	1	6	3	..	1 (morphin)
Chorea cases	15	1	9	4	1	..

RESULTS IN CHOREA CASES

The chorea cases (Table 4) proved unexpectedly to be of great interest to us. It will be seen from the table that nine of the fifteen cases had accelerated reactions, and that one had a slightly accelerated Kottmann reaction. Only four were normal, while one was slightly retarded. Of the normal reactions, two occurred in mild cases, and one in a convalescent. The third was obtained in a case which was mild on admission, but which became worse later and then gave an accelerated reaction. This child improved after a time, and again gave an accelerated reaction, but when she developed an acute tonsillitis with exacerbation of the choreiform movements, the Kottmann reaction was again accelerated. The child with the slightly retarded reaction had a mild case and was in the convalescent stage. On analyzing these results, then, we found that the severe or moderate cases of chorea consistently showed accelerated Kottmann reactions.

In order to observe the effect of the Kottmann reaction of thyroid administration by mouth, we selected one of these children as an experimental subject, merely because he was likely to be in the hospital for some time. He had already been in hospital over a month under the usual treatment of isolation and high calory diet, with no abatement of his symptoms. After thyroid extract had been given for three days, there was a marked diminution in his formerly incessant movements, and within a week he appeared perfectly normal. This was confirmed by several observers. As a result, thyroid was given in eight other cases, and equally striking results were obtained in five. The three other children had the type of chorea in which extreme weakness and psychic disturbance are the predominating symptoms. One of them was a 5-year-old girl who, on admission to the hospital a month before, was unable to sit up. At the time thyroid was started, she was improved to the extent that she could sit up alone, but still had choreic movements and was very weak. After receiving thyroid for nearly three weeks, she seemed better but was unable to stand. The dose was therefore increased, and three days later, the child was found walking up and down her bed entirely unsupported. Whether this was a result of thyroid therapy or a coincidence we are not willing to say, but from that time on improvement was rapid. At present, twelve children with chorea have been or are being treated with thyroid. It is still far too early to make any statements as to the results of this method of treatment, or as to suitable dosage.

If, as Petersen suggested, the Kottmann reaction is a reflection of the increased metabolism which occurs with hyperthyroidism, then an accelerated reaction would be expected, with a decreased basal metabolism. In a condition such as chorea, in which the patient is in almost constant motion, we would anticipate an increased basal metabolism. This, however, would be difficult if not impossible to determine. If this reasoning is correct, the administration of thyroid to these patients is not a reasonable procedure; but, on the other hand, we have the evidence of accelerated Kottmann reactions. Other factors are doubtless involved, such as disturbance of the nervous system from an abnormal physiologic condition of the glands of internal secretion. The field of speculation which has thus been opened is a wide one, demanding careful study. With the clues thus furnished us from this preliminary work, we are now studying chorea particularly from this point of view. As yet, we can say little about dosage, but this is being carefully considered, as well as the advantages of using various preparations of thyroid, such as thyroxin, thyroid extract and thyroid residue. The indications are that the cases characterized by great weakness and psychic disturbance require larger doses of thyroid. We realize that our findings are far from conclusive, but we feel that the results of this method of treatment have been sufficiently striking to warrant at least a hope that we have chanced on a way to shorten the course of chorea. The final test will be a comparison of the disease in those patients who have been given the ordinary treatment with those who have in addition received thyroid.

SUMMARY

The Kottmann test was performed on 106 children.

Twenty-eight children presenting miscellaneous conditions were chosen as controls, of whom twenty-one were normal. Of the three retarded reactions, two could be explained on the basis of medication (sodium bromid and calcium chlorid).

Of thirty-three cases of acute infection, only thirteen gave normal Kottmann reactions.

The group of endocrine cases was unsatisfactory, and no conclusions could be drawn from the results.

In the group of cardiac cases, the predominating reaction was acceleration, probably from the lowered vitality of the children.

Because of the findings in the fifteen cases of chorea, administration of thyroid is suggested as a possible aid in treatment.

THE TREATMENT OF INFANTILE TETANY WITH ULTRAVIOLET RADIATION

ITS EFFECT ON THE CLINICAL SYMPTOMS AND ON THE CALCIUM CONCENTRATION IN THE BLOOD SERUM *

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As a result of the many investigations on the pathogenesis of infantile tetany, various remedial agents have been suggested for its treatment. Temporary starvation, catharsis and change from cow's milk to maternal milk have all been employed, but at present are usually considered accessory to more potent measures. The effect of cod liver oil with and without phosphorus has been more completely studied, and gradual but rather slow improvement demonstrated. Howland and Marriott,[1] in 1918, placed the therapeutic use of calcium on a scientific basis by showing that, in active infantile tetany, the calcium concentration in the blood serum is uniformly low and that this concentration can be increased by the administration of sufficient doses of calcium salts. It is a recognized fact that, even with combined cod liver oil and calcium therapy, the return of the serum calcium to a normal figure may be very slow, although the clinical findings of tetany may disappear fairly promptly (as in Case D. G., Table 3). The demonstration of a low concentration of calcium in the blood serum is therefore a valuable aid in the diagnosis of infantile tetany, and the demonstration of its return to normal is probably the most reliable sign of the cure of the disease.

OPINION OF OTHERS AS TO TREATMENT

Many clinicians have felt that the chlorid of calcium is more effective than the lactate in the treatment of infantile tetany, and Howland and Marriott [1] substantiated this clinical impression. This observed fact has been proved by Gamble and Ross [2] to be due to the unoxidizable chlorin-ion (Cl). This is in agreement with the fact demonstrated by Scheer [3] that placing hydrochloric acid in the milk will cause the

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* Received for publication, June 12, 1923.

* From the Infant's Hospital, The Children's Hospital and the Department of Pediatrics, Harvard Medical School.

[1] Howland, John, and Marriott, W. McK.: Quart. J. Med. **11**:289 (July) 1918.

[2] Gamble, J. L., and Ross, G. S.: Studies of Tetany. II, Am. J. Dis. Child. **25**:470 (June) 1923.

[3] Scheer, K.: Jahrb. f. Kinderh. **97**:130 (Feb.) 1922.

symptoms of infantile tetany to disappear, and is also in agreement with the finding of Freudenberg and György[4] that the same result follows the administration of ammonium chlorid. Freudenberg and György[5] assumed that the therapeutic action of ammonium chlorid was due to the acid effect which Haldane[6] has demonstrated that this salt produces. Gamble and Ross have shown that ingestion of calcium chlorid, hydrochloric acid or ammonium chlorid produces the same acid effect in the body, this effect consisting of a reduction of the plasma bicarbonate due directly to an increase in the chlorids, and an elevation of the hydrogen-ion concentration of the plasma. On the basis of data published by Rona and Takahashi[7] in 1913, Freudenberg and György pointed out that a reduction of the bicarbonate and an increase in the hydrogen-ion concentration in the plasma might be expected to increase the ionized fraction of the total calcium content of the plasma. This increase in effective calcium should decrease the hyperirritability of the neuromuscular apparatus.

The relief of the symptoms of infantile tetany by the methods mentioned is either slow, with a rather long period of active symptoms; or when the hydrochloric acid producing substances are used, it is rapid but of short duration, the hyperirritability tending to recur very soon after cessation of medication. A procedure leading to more permanent results would be very acceptable in the treatment of the disease. The fact that tetany usually occurs in late winter and early spring, when the concentration of the actinic rays of the sun is low, and is spontaneously cured in the early summer, suggested an investigation of the effects produced by the use of ultraviolet radiation. Climatic conditions precluded the employment of the sun's rays. Park[8] and others have shown that, in rickets at least, the effect of cod liver oil in curing or protecting against the disease is the same as that secured by the use of sunlight. Because of this interchangeable effect on an associated disease, a few patients with active tetany symptoms and some with a low serum calcium concentration accompanying rickets were given varying doses of cod liver oil, to serve as comparison cases.

Huldschinsky,[9] considering infantile tetany as a manifestation, in the nervous system, of rickets, showed, in 1920, that this "cerebral rickets" could be relieved by the use of ultraviolet rays in the same way that he had already proved the bone pathology to be influenced.

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[4] Freudenberg, E., and György, P.: Klin. Wchnschr. **1**:410 (Feb. 25) 1922.

[5] Freudenberg, E., and György, P.: Jahrb. f. Kinderh. **96**:5, 1921. Freudenberg, E., and György, P.: Klin. Wchnschr. **1**:222 (Jan. 28) 1922.

[6] Haldane, J. B. S.: J. Physiol. **55**:265 (Aug.) 1921.

[7] Rona, P., and Takahashi, D.: Biochem. Ztschr. **49**:370, 1913.

[8] Park, E. A.: Physiol. Rev. **3**:106 (Jan.) 1923.

[9] Huldschinsky, K.: Ztschr. f. Kinderh. **26**:207 (Sept.) 1920.

Sachs[10] reported independently, and at the same time, the clinical cure of seven cases of latent infantile tetany by the employment of artificial sunlight, and later, he[11] published the records of eight patients clinically cured of active tetany by the same means. Both authors used as their criteria for diagnosis and improvement the mechanical and electrical hyperirritability of peripheral nerves. The only published observations concerning the effect of ultraviolet radiation on serum calcium were reported nearly simultaneously by Tisdall[12] and Kramer, Casparis and Howland,[13] working on the inorganic phosphorus and calcium content of the serum in cases of healing rickets. The latter authors record one case of infantile tetany, in which, however, calcium therapy had been employed for nearly one month before active ultraviolet irradiation began. Ten of the total of eleven reported cases of rickets showed an increase in the serum calcium concentration under artificial heliotherapy, this being coincident with the inorganic phosphorus increase. In none of the cases was the serum calcium below 8 mg. in 100 c.c. at the beginning of treatment.

PRESENT STUDY OF CASES

The present study is based on eleven cases of infantile tetany treated with ultraviolet rays and four comparison cases selected from among those patients who received cod liver oil. The usual criteria of mechanical and electrical hyperirritability, accompanied by a low serum calcium concentration, were used in making the diagnosis and following the progress. The demonstration of mechanical hyperirritability consisted in eliciting an appropriate muscular contraction by tapping the trunk of the facial nerve (facial phenomenon of Chvostek) or the peroneal nerve, or producing carpal spasm by compression of the upper arm (Trousseau). The electrical irritability was studied in the usual way with the galvanic current (Erb's test). A cathodal opening contraction (COC), or, in its place, a cathodal closing tetany (CCT), below 5 milliamperes was considered as the electrical sign of greatest diagnostic importance. In the presence of such a finding, the anodal opening contraction (AOC) was obtained with less current than the anodal closing contraction (ACC), the so-called reversal of anodes (AOC $<$ ACC). The occurrence of this latter phenomenon, even in the absence of a cathodal opening contraction (COC) below 5 milliamperes, was considered as suggestive evidence for the diagnosis of latent tetany.

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[10] Sachs, F.: Jahrb. f. Kinderh. **93**:167, 1921.

[11] Sachs, F.: München. med. Wchnschr. **68**:984 (Aug. 5) 1921.

[12] Tisdall, F. F.: Canad. M. A. J. **12**:536 (Aug.) 1922.

[13] Kramer, Benjamin; Casparis, H. R., and Howland, John: Ultraviolet Radiation in Rickets, Am. J. Dis. Child. **24**:20 (July) 1922.

Those patients who came with a history of very recent convulsions, carpopedal spasm or laryngospasm, or showed these symptoms in the hospital, and who had a serum calcium below 7 mg. in 100 c.c., were classified as active cases (Table 1). Those patients without manifest symptoms, but who showed recognizable hyperirritabiliy signs, were classified as latent cases (Table 2). The latter varied greatly in severity, two having a moderately low serum calcium concentration with no signs of hyperirritability but reversal of the anodes in Erb's test.

The criterion used to indicate complete cure of the disease was the return of the blood serum calcium concentration to practically the normal figure of 10 mg. in 100 c.c., with the method published by Kramer and Tisdall [14] in 1921. As was previously pointed out, this standard is more exacting than the clinical estimation of a cure. In some of the later cases, measurements were made of the inorganic phosphorus concentration in the serum by the method of Tisdall,[15] or in the whole blood by the method of Bell and Doisy.[16]

The source of the ultraviolet rays was an all-mercury electrode, quartz-encased burner, using 4 amperes on a 110-volt direct circuit. The age of this lamp was between 100 and 200 production hours during the course of this study. About 65 to 67 per cent. of the total radiation of this type of burner consists of ultraviolet rays. Although the spectrum of the particular burner used was not studied, Coblentz [17] has shown that the liquid mercury electrode burner produces ultraviolet radiation with the most intense spectral lines at 365, 405, 314 and 302 millimicrons in decreasing magnitude. Hess and Weinstock [18] have recently shown that the rays with a wave length of 302 millimicrons or less are the most active in their curative and protective effects on rats living under a rickets producing regimen. In this connection, it is interesting to note that the intensity of the sun's ultraviolet spectrum as analyzed by Abbott and Fowle [19] closely approaches zero at a wavelength of 300 millimicrons.

TECHNIC

The patients all were exposed with the lamp at a uniform and unvarying distance of 50 cm. from the surface of the body. The initial treatment was usually two minutes to the front and two minutes to the back of the body (total of four minutes), and this was increased one minute to the front and to the back daily (total increase of two minutes), unless contraindicated by erythema. The maximum total exposure in this clinic never exceeds forty minutes daily, and this was not reached in any of the cases studied. The skin of a few of the patients became moderately pigmented, and nearly all of them showed slight desquamation at some stage of the treatment. The burner used was shown, near the end of the series, to produce a mild erythema of the previously unexposed skin of an infant's abdomen in four minutes at a distance of 50 cm.

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[14] Kramer, Benjamin, and Tisdall, F. F.: J. Biol. Chem. **47**:475 (Aug.) 1921.

[15] Tisdall, F. F.: J. Biol. Chem. **50**:329 (Feb.) 1922.

[16] Bell, R. D., and Doisy, E. A.: J. Biol. Chem. **44**:55 (Oct.) 1920.

[17] Coblentz, W. W.: Am. J. Electrother. & Radiol. **39**:395 (Oct.) 1921.

[18] Hess, A. H., and Weinstock, Mildred: Study of Light Waves in Their Relation to Rickets, J. A. M. A. **80**:687 (March 10) 1923.

[19] Abbott and Fowle: Ann. Astrophys. Obs. **2**:104, 1908.

Table 1.—*Active Cases of Infantile Tetany Treated with the Mercury Vapor Quartz Lamp at a Distance of 50 Cm.**

Patient, Age and Color	Date, 1923	Symptoms	Electrical Reaction. Milliamperes	Mg. in 100 C.c.		Total Minutes Treatment
				Ca	P	
P. B. 5 mo. White	3/28	Conv., fac. 0, crow +	CCT 5.0, AOC < ACC	5.5	—	0
	4/ 4	Fac. ±, crow 0	CCT 7.0, AOC < ACO	—	—	10
	4/ 6	None	COC 7+, AOC < ACQ	8.4	—	20
	4/10	None	COC 7+, ACC < AOO	9.3	—	64
M. S. 8½ mo. White	4/15	Conv., crow 0, fac. ±	CCT 5.0, AOC < ACO	6.8	—	0
	4/19	Fac. ±, no conv.	CCT 6.5, AOC < ACO	—	—	18
	4/23	None	COC 7+, AOC = ACC	8.5	—	40
	4/28	None	COC 8+, ACC < AOO	9.6	—	74
R. C. 9 mo. White	4/25	Conv., fac. +, Trou. +	CCT 2.5, AOC < ACC	5.4	—	0
	4/28	Conv., fac. +, crow +	CCT 3.5, AOO < ACC	—	—	18
	4/30	Fac. ±, crow +	CCT 5.0, AOC < ACO	6.6	—	26
	5/ 4	Crow +	CCT 7.0, AOO < ACO	8.0	4.1(WB)	94
	5/11	None	COO 7+, ACO < AOO	9.5	6.0(WB)	224
	5/18	None	COC 7+, ACC < AOC	10.0	—	224
D. A. 5 mo. White	5/ 4	Laryngospasm, fac. +, Trou. +	COC 2.5, AOO < ACC	5.4	6.4(WB)	0
	5/ 8	Fac. +, crow +	COC 7.5, AOC < ACC	—	—	18
	5/11	Fac. 0, crow ±	COC 6.0, AOO < ACO	7.7	8.1(WB)	38
	5/17	None	COO 7+, ACO < AOO	9.8	6.2(S)	110
C. R. 12 mo. White	5/10	Conv., fac. +, crow +, Trou. +	COO 3.0, AOO < ACO	5.9	5.8(WB) 8.1(S)	0
	5/14	Crow +, fac. ±	—	7.9	—	26
	5/18	None	COC 7+, AOC < ACO	—	6.4(S)	66
	5/23	None	COC 7+, ACO < AOC	8.1	8.3(S)	94
	5/28	None	—	9.7	6.8(S)	250
A. R. 6 mo. Colored	5/14	Conv., fac. +, crow +, Trou. +	CCT 3.5, AOC < ACC	—	6.3(S)	0
	5/15	Crow, fac., Trou. +	CCT 6.0, AOC < ACC	5.2	—	6
	5/18	Crow, Trou. ±, fac, 0	CCT 7.0, AOC < ACC	7.5	—	34
	5/23	None	COC 7+, AOC = ACC	7.8	6.6(S)	114
	5/28	None	COC 7+, AOC = ACC	9.3	—	244

* In the tables, Ca = calcium; P = inorganic phosphorus; conv. = convulsion; fac. = facial phenomenon (Chvostek); Trou. = Trousseau's phenomenon; CCT = cathodal closing tetany; COC = cathodal opening contraction; AOC < ACC = anodal opening contraction with less current than anodal closing contraction; (WB) = whole blood; (S) = serum; HCl = hydrochloric acid; C.L.O. = cod liver oil; $CaCl_2$ = calcium chlorid; NH_4Cl = ammonium chlorid.

None of the eleven patients treated received cod liver oil, calcium, ammonium chlorid or other medication directed toward the relief of the tetany. They were kept away from open windows and were not taken out doors. All received whole cow's milk or its indicated dilution, and those of proper age received cereal. Green vegetables and orange juice were withheld during the immediate period of observation.

The progress of the active cases of infantile tetany treated with ultraviolet radiation is recorded in Table 1, and the latent cases in Table 2. The data on two patients with active teany who received cod liver oil are given in Table 3. In Table 4 are recorded the calcium determinations on the blood of two patients with rickets who showed moderately low serum calcium concentrations and who were also receiving cod liver oil.

Table 2.—*Latent Cases of Infantile Tetany Treated with the Mercury Vapor Quartz Lamp at a Distance of 50 Cm.*

Patient, Age and Color	Date, 1923	Symptoms	Electrical Reaction, Milliamperes	Mg. in 100 C.c.		Total Minutes Treatment
				Ca	P	
C. McG. 6 mo. White	4/ 3	Crow +, fac. +	CCT 2.5, AOC < ACO	6.9	—	0
	4/ 6	None	CCT 5.0, AOC = ACC	—	—	12
	4/10	None	COC 7+, AOC = ACO	8.9	—	48
	4/15	None	COO 7+, ACC < AOC	—	—	64
	4/20	None	COO 7+, ACC < AOC	10.7	—	126
	5/11	None	COC 7+, ACC < AOC	10.3	7.6(S)	378
S. S. 3½ mo. White	5/ 3	Crow +, fac. +, Trou. +	OCT 5.0, AOC < ACO	7.4	5.5(WB)	0
	5/ 5	Crow +, fac. +, Trou. ±	—	7.6	—	4
	5/11	None	COC 7+, ACO < AOO	8.6	5.1(WB) 5.4(S)	54
	5/18	None	COC 7+, ACC < AOO	9.4	6.7(S)	142
	5/22	None	—	10.5	—	242
S. P. 9 mo. White	5/ 4	None	COO 5.0, AOC < ACO	6.2	3.4(WB)	0
	5/ 8	None	COO 7+, AOC < ACO	—	—	10
	5/11	None	COC 7+, AOC < ACO	7.4	4.3(WB) 6.3(S)	40
	5/18	None	COC 7+, AOC = ACO	8.8	6.0(S)	142
	5/23	None	—	9.5	—	186
U. W. 12 mo. Colored	5/ 7	None	COC 7+, AOC < ACC	6.9	—	0
	5/ 8	None	OOC 7+, AOC < ACO	7.2	2.1(WB)	0
	5/14	None	—	8.3	2.7(WB)	58
	5/18	None	COC 7+, AOC = ACC	8.6	5.7(S)	112
	5/23	None	COC 7+, ACC < AOC	8.8	4.2(S)	192
	5/28	None	COO 7+, ACC 7+, AOC 7+	9.9	—	300
S. R. 2¼ yr. White	5/10	Crow +, fac. ±	COC 7+, AOC < ACO	6.7	4.7(WB) 6.3(S)	0
	5/14	Crow +, fac. 0	—	6.1	6.5(S)	10
	5/17	Skin erythema	—	—	—	28
	5/18	Skin erythema	COC 7+, AOC = ACC	—	—	32
	5/23	None	COC 7+, ACO < AOC	8.9	6.4(S)	37
	5/28	None	—	9.5	6.4(S)	76

RESULTS

The six active cases of infantile tetany (Table 1) all showed steady clinical improvement with ultraviolet irradiations, as evidenced by the relief of symptoms and the decrease in mechanical and electrical hyperirritability. Only one patient had a convulsion after the first treatment, and this was inadvertently induced by a gastric lavage. The clinical improvement was paralleled by the steady increase in serum calcium concentration. This had reached a practically normal figure in each patient at the time of discharge or when the observations were discontinued. With the mercury vapor lamp at the uniform distance of 50 cm., the total length of exposure necessary to cause an increase of 1 mg. of calcium in 100 c.c. of serum varied from seventeen to sixty-five minutes, with an average of forty-one minutes. The rise of calcium was proportionately more rapid in those patients who had the lowest concentrations in the serum at the beginning of the irradiations. The average number of days under treatment was thirteen. The mechanical hyperirritability symptoms disappeared in from four to eight days.

Table 3.—*Active Cases of Infantile Tetany Treated with Cod Liver Oil*

Patient, Age and Color	Date, 1923	Symptoms	Electrical Reaction, Milliamperes	Medication	Ca. Mg. in 100 C.c.
A. C. 4 mo. White	2/20	Conv., carpopedal spasm	CCT 2.0, AOC < ACC	None	5.6
	2/22	Same	—	HCl, 630 c.c. tenth normal daily	—
	2/24	No conv., Trou. 0	COC 7+, AOC < ACC	Omitted	—
	3/ 1	Fac. +, Trou. +	CCT 2.5, AOC < ACC	Lactic acid milk; C. L. O., 4 c.c. daily	7.1
	3/26	None	COC 6.0, ACC < AOC	Same	8.8
	3/30	None	CCT 5.5, AOC < ACC	Same	8.7
	4/23	None	—	Same	9.4
	5/22	None	—	Same	10.0
D. G. 16 mo. White	2/22	Crow +, fac. +, Trou. +, per. +	COC 3.0, AOC < ACC	None	6.3
	2/23	Same	COC 2.5, AOC < ACC	NH_4Cl, 3.5 gm. daily	—
	2/26	Crow +, fac. 0, Trou. 0, per. 0	COC 7+, ACC < AOC	Omitted	7.3
	3/ 1	Crow, Trou., fac. +	COC 3.0, AOC < ACC	None except lactic acid milk	5.4
	3/10	Crow +	COC 7+, ACC < AOC	C. L. O., 4 c.c. daily	—
	3/16	Crow +, fac. +	—	Same	5.6
	3/21	Crow +	CCT 7.5, AOC = ACC	Same	6.6
	3/26	Crow +	COC 5.0, ACC < AOC	Same plus $CaCl_2$, 3.7 gm. daily	5.6
	3/30	Crow +	COC 7+, ACC < AOC	$CaCl_2$ omitted	6.2
	5/15	Crow +, fac. 0	COC 7+, AOC < ACC	C. L. O., 4 c.c. daily	8.4

The five latent cases (Table 2) showed the same steady improvement in symptoms and the same tendency toward an increase in the concentration of the serum calcium. The rate of this increase was somewhat slower than in the active cases. The total duration of exposure required to produce an average rise of 1 mg. of calcium in 100 c.c. of serum varied from twenty-seven to one hundred minutes, and averaged sixty minutes. The average number of days of treatment was sixteen. Because of a distinct erythema which developed in S. R., exposures had to be omitted for several days and the stay in the hospital was prolonged. U. W., a colored baby, showed the slowest rise in calcium concentration.

A. C. (Table 3) showed a gradual rise in calcium from 7.1 mg. to 10.0 mg. in 100 c.c. of serum during the course of two and three-fourths months. The diet was lactic acid milk and the treatment was 60 minims (4 c.c.) of cod liver oil daily during this period. The data also show the rapid clinical improvement resulting from the administration of hydrochloric acid in the milk (2-24, Table 3). D. G. showed a rapid initial improvement in clinical symptoms following the ingestion of ammonium chlorid, but he failed to maintain this condition when administration of the salt was stopped. During the two and one half months in which he received 60 minims (4 c.c.) of cod liver oil daily, the calcium advanced from 5.4 mg. to 8.4 mg. in 100 c.c. of serum. During five days of this time, he received 55 grains (3.7 gm.) of calcium chlorid daily, with a resulting increase in serum calcium of only 0.6 mg. in 100 c.c. It is interesting to note that the early part of the treatment of these two cases preceded the investigation of the effect of ultraviolet rays on tetany, so the two groups were under different climatic conditions. D. G., however, still had a low serum calcium figure, a crow and a reversal of the anodal reaction, May 15, which was at practically the end of the period of observation on the artificial heliotherapy cases.

Table 4.—*Cases wtih Low Serum Calcium Accompanying Rickets, Treated with Cod Liver Oil*

Patient, Age and Color	Date, 1923	Symptoms of Tetany	Electrical Reaction, Milliamperes	Medication	Ca, Mg. in 100 C.c.
A. V. 12 mo. White	5/ 4	None	—	C. L. O., 1 c.c. daily	7.6
	5/11	None	COC 7+, AOC < ACC	Same	—
	5/15	None	—	C. L. O., 8 c.c. daily	—
	5/18	None	COC 7+, AOC < ACC	Same	7.9
J. H., 8 mo. White	5/ 4	None	COC 7+, AOC = ACC	C. L. O., 4 c.c. daily	8.4
	5/18	None	COC 7+, ACO < AOC	Same	8.4

J. H. and A. V. (Table 4) had cases of rickets accompanied by a moderate lowering of the serum calcium concentration and changes in the anodal electrical reactions. They were selected to serve as controls because the lack of severe symptoms of tetany made active treatment unnecessary, and because they were under the same ward conditions at the same time as the patients receiving ultraviolet irradiations. Both of these patients failed to show a very appreciable rise of serum calcium in a period of time comparable to that required for the cure of infantile tetany by the use of artificial heliotherapy. Although Park[8] has proved that the effect of cod liver oil and sunlight on rickets is the same and interchangeable, the cure of infantile tetany by cod liver oil in the cases studied was much slower than with the ultraviolet rays. It is realized, however, that the small number of cases and the use of rather small doses of a cod liver oil with unknown vitamin content preclude the formation of any definite conclusions.

SUMMARY

Because infantile tetany is only temporarily improved by the use of hydrochloric acid producing substances (calcium chlorid, ammonium chlorid and hydrochloric acid), an investigation of two agents which might be expected to give more permanent relief was undertaken. The exacting standard of a return of the serum calcium concentration to 9.5 or 10.0 mg. in 100 c.c. was used to judge the completeness of the cure. Cod liver oil caused a gradual increase in the calcium of the serum over a period of several weeks. In eleven patients with infantile tetany, ultraviolet rays applied in amounts approaching the limit of tolerance, and unaccompanied by other treatment, caused a progressive and permanent relief of the clinical symptoms, paralleled by the return of the serum calcium concentration to an essentially normal figure. With the mercury vapor lamp at a distance of 50 cm., the average total exposure necessary to cause an increase of serum calcium of 1.0 mg. in 100 c.c. was fifty minutes. An average of fourteen days was required for the calcium to rise from its initial low figure to about 9.5 mg. in 100 c.c. of serum. This rise was proportionally more rapid in the cases having the lowest initial concentration of calcium.

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KIDNEY FUNCTION IN ACUTE DISEASE *

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In 1918, Frothingham,[1] writing on kidney function as affected by the acute infectious diseases, raised the question as to whether patients without apparent renal involvement would show disturbed kidney function if subjected to proper tests. To determine this, something more than clinical observation is necessary, as indicated by Morse,[2] in 1922, who, in discussing the correlation of clinical and pathologic findings in nephritis, states his belief that the clinical findings and pathologic anatomy do not agree at all well and that kidney lesions cannot be interpreted in terms of apparent function.

An illustration of this independence of the clinical and pathologic aspect is found in Veil's [3] analysis of congenital cystic kidney, by which he demonstrated that the function may remain normal in all respects in this condition.

Reports appear in the literature of the last ten years concerning unusual findings in sick children which might have found satisfactory explanation if disturbed kidney function could have been demonstrated. Of two children with pyelitis,[4] one died with no adequate cause of death other than asthenia. Perhaps a retention and consequent toxemia from reflex impairment of the kidney will explain the fatal outcome. Another developed complete suppression for a period of five days; positive evidence of kidney dysfunction, as may well be another report [5] relating an unexplained oliguria of five days' duration, without albumin or casts, occurring as a complication of colitis.

In a paper on infection of the kidney pelvis, with rise in temperature and systemic disturbance, Ramsey [6] divided his cases into two

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[1] Frothingham, Channing: Studies on Renal Function, Arch. Int. Med. **22**:74 (July) 1918.

[2] Morse, P. F.: Am. J. M. Sc. **163**:697 (May) 1922.

[3] Veil, W. H.: Deutsch. Arch. f. klin. Med. **115**:156, 1914.

[4] Freeman, R. G.: Tr. Am. Pediat. Soc., 1919.

[5] Freeman, R. G.: Arch. Pediat. **36**:367, 1919.

[6] Ramsey: Tr. Am. Pediat. Soc., 1922.

groups: (1) those children who throughout the course of the disease played normally and were evidently not consciously affected, and (2) those children who were plainly sick from the disease. No satisfactory explanation of the difference in these two groups was offered.

These are examples of instances in which incomplete diagnosis may have been due to lack of appreciation of the frequency of kidney embarrassment in acute infections. Our own figures in pyelitis indicate the gravity of this embarrassment.

Evidence of such kidney disturbance has been brought out in Schloss'[7] study of intestinal intoxication in infants, in which he demonstrated a remarkable degree of nitrogen retention existing in cases of intoxication, entirely independent of blood concentration or accompanying primary nephritis. Using a method giving consistently higher figures than that of Folin, he showed that, while the nonprotein nitrogen of normal infants' blood ranged from 23 to 39 mg., in forty-four infants suffering from intoxication, the nonprotein nitrogen ranged from 57 to 232 mg. That the increase in nitrogenous elements of the blood was not due to concentration was shown by the absence of any increased corpuscular volume.

These observations were later confirmed by the work of Schwarz and Kohn.[8]

As further evidence of kidney dysfunction, Schloss found the elimination of phenolsulphonephthalein in thirty children suffering from intoxication to be from 4 to 38 per cent., as compared with from 58 to 94 per cent. in normal infants of the same age.

In the fall of 1920, a child, long treated for cystitis and colitis in other institutions, was admitted to the Children's Medical Division of Bellevue Hospital. The urine was alkaline, and contained pus and albumin. The fluoroscope revealed a large vesicle calculus.

The phenolsulphonephthalein test showed elimination of 13 per cent. the first hour, and of 15 per cent. the second hour. Mosenthal's test showed fixation at medium low level, with small total excretion.

Twenty-eight days after the removal of the stone, the urine was normal. The phenolsulphonephthalein excretion was 45 per cent. the first hour and 30 per cent. the second hour. The Mosenthal test showed no fixation. This case is an example of a number of similar instances of apparent serious inhibition of kidney function which have stimulated our interest in the subject.

In addition to the foregoing evidence of a purely clinical and chemical nature, the work of Councilman,[9] in 1898, is of interest from the point of view of pathology. During a period of two and one half years, he observed and described forty-two cases of acute interstitial nephritis occurring in children who had died of diphtheria, measles, whooping cough, empyemia, pneumonia or meningitis, and who had shown no clinical evidence of kidney damage during life.

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[7] Schloss, O. M.: Intestinal Intoxication in Infants, Am. J. Dis. Child. **15**:165 (March) 1918.

[8] Schwarz, Herman, and Kohn, J. L.: Infant of Low Birth Weight; Its Growth and Development, Am. J. Dis. Child. **31**:291 (March) 1921.

[9] Councilman: J. Exper. Med. **3,** 1898.

If infants suffering from intestinal intoxication show consistently such marked retention as Schloss' figures indicate; if there may be such dysfunction accompanying a pelvis infection as our case of pyelitis gave evidence of, and with such anatomic evidence of actual nephritis in the acute infectious diseases, it seems profitable to attempt to learn something more definite in regard to kidney function in a number of other diseases.

As stated by Morse, the appreciation and management of the individual case must depend on the evaluation of each part of the kidney mechanism. Information obtained from examination of the urine alone is not sufficient for this purpose. The presence of albumin and casts in the urine does not necessarily indicate impaired kidney function, nor is their absence a guarantee of a normally functioning kidney.

BASIS OF AUTHOR'S STUDY

We have therefore undertaken this study of kidney function in acute disease, basing it on the information to be gathered from the phenolsulphonephthalein test; the fixation test as modified by Mosenthal, and a study of the chemistry of the blood.

The Phenolsulphonephthalein Test.—From our findings in the study of kidney function in children with nephritis, it is not possible to generalize about the results of this test, except in cases of acute hemorrhagic nephritis. In these, the output was low in the beginning of the disease and rose gradually, with a concomitant drop to normal of the metabolites in the blood. The output did not become normal, however, for some time, in a few cases months, after all clinical and urinary signs had disappeared, and the blood constituents had become normal.

In the chronic cases, the findings were different, and the blood chemistry findings did not always parallel the results of the phenolsulphonephthalein test. One patient who came to us with a retention in the blood of 111 mg. of nonprotein nitrogen had at that time an output of 5 per cent. This rose gradually to 25 per cent., when the nonprotein nitrogen dropped to 96 mg., with a uric acid of 6.2. After this, the phenolsulphonephthalein output remained at 25 per cent., although the uric acid became normal in amount and the nonprotein nitrogen at one time fell to 45 mg. This child passed enormous quantities of urine, and, in spite of these findings, did very well clinically during the time she was under observation.

In contrast to this case is one in which the patient constantly had a phenolsulphonephthalein output of from 45 to 50 per cent., in spite of nonprotein nitrogen retention varying from 60 to 80 mg., and on only two occasions being as low as from 40 to 45 mg. The uric acid was always from 4 to 5 mg. Another child, who clinically seemed to have a more severe condition, with marked edema and low output of urine, had practically normal metabolites and a phenolsulphonephthalein output usually of from 45 to 70 per cent. It seems then that, in the ordinary case of acute nephritis in childhood, the phenolsulphonephthalein test is a fair index of kidney function and when made repeatedly during the course of the disease gives sufficiently accurate evidence as to the recovery of the kidney. The findings in the chronic cases, on the other hand, lead us to be guarded in basing a prognosis on the results of the phenolsulphonephthalein test, and we feel that the blood chemistry findings are of more value as an indication of the functioning not only of the kidneys but also of the whole body metabolism.

Leopold and Burkhart [10] place the range of phenolsulphonephthalein excretion in normal children at from 50 to 90 per cent., an average of 70 per cent. Tileston and Comfort [11] give an even higher average (80 per cent.).

Over a period of years on the Children's Medical Division, the phenolsulphonephthalein output in normal children averaged 60 per cent.; in the early stages of acute nephritis, 10 per cent., in chronic nephritis 40 per cent. The lowest figure was 5 per cent., the highest, 95 per cent. In thirty-four infections, the output was below 50 per cent. in twenty cases, or 60 per cent. of cases. The average output was 39.3 per cent.

Fixation of Specific Gravity.—In the cases of chronic nephritis, the urine had a low fixation of gravity; i. e., around 1.010. One child who had at first a high fixation, around 1.020 to 1.025, later, in the acute stage, had a normal variation; but finally came back to the hospital as a chronic nephritic. In only 33 per cent. of the cases of acute hemorrhagic nephritis was there a fixation of gravity in the first part of the disease, and this later disappeared. The other patients all had a normal variation from the beginning.

As a method of interpretation of the condition of the kidney function in chronic nephritis, it is of disinct value in children.

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[10] Leopold, J. S., and Burkhart, Adolph: Nonprotein Nitrogen Constituents of the Blood and the Phenolsulphonephthalein Test in Children, Am. J. Dis. Child. **11**:432 (June) 1916.

[11] Tileston, Wilder, and Comfort, C. W.: Total Nonprotein Nitrogen and the Urea of the Blood, and the Phenolsulphonephthalein Excretion in Children, Am. J. Dis. Child. **10**:278 (Oct.) 1915.

The Chemistry of the Blood.—By this means, the most reliable information is obtained as to the reaction of the kidney to acute infections.

Methods: In determining nonprotein nitrogen, uric acid and creatinin, the system of Folin and Wu was followed.[12] The earlier uric acid determinations were made by Folin's first method; the later ones were made by his modified method, introduced in 1922.[13]

We realize that what is determined as creatinin is possibly not creatinin, but the significance of the color producing substance remains the same. We have put the upper normal limit for creatinin at 2; for nonprotein nitrogen at 35, and for uric acid at 3.5. These limits may seem too low in view of some figures published for adults; but we think that in normal children the levels are constantly lower than in adults. In our studies of nephritis, we found a creatinin of 2 mg. to be of more significance than it would be in an adult.

The group of infections studied includes: thirty cases of pneumonia in patients under 2 years of age; forty cases in patients over 2 years of age; five cases of bronchitis; twelve, pulmonary, glandular and miliary tuberculosis; ten, tuberculous meningitis; eleven, epidemic (lethargic) encephalitis; sixteen, tonsillitis; forty-three, chorea; twenty-six, miscellaneous infections; twelve, postoperative, noninfectious.

Blood chemistry in normal children: In 1917, Meyers and Chapin [14] published figures on the blood chemistry of 149 children. Their values are similar to those obtained in adults, but slightly lower. They conclude that the kidney of the child is more efficient and that nitrogen retention is less quick to develop. Folin's [15] figures in 1922, on twelve young men, were: nonprotein nitrogen, minimum 27.8, maximum 39.4, average 32.1; uric acid, between 0.7 to 3.0. This was found to be subject to great variations normally. Creatinin was remarkably constant, at from 1.2 to 1.5.

Our figures for ninety-one normal children (without evidence of acute infection), aged from 1 month to 13 years, correspond to the foregoing, and are shown in the accompanying table.

If these figures were grouped according to age, the children of 2 years and under would show a slightly lower average for nonprotein nitrogen (about 26 mg.). The figures for uric acid and creatinin would not change materially.

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[12] Folin, O., and Wu, H.: J. Biol. Chem. **38**:81 (May) 1919.

[13] Folin, O., and Wu, H.: J. Biol. Chem. **54**:2, 1922.

[14] Chapin, H. D., and Meyers, U. C.: Chemical Examination of the Blood in Children, Am. J. Dis. Child. **18**:555 (Dec.) 1919.

[15] Folin, O., and Wu, H.: Physiol. Rev., 1922.

Table 1.—*Ninety-One Normal Cases*

Case	Age	Sex*	Non-protein Nitrogen	Uric Acid	Creatinin	Retention, per Cent.	Urine	Diagnosis
226	10 yr.	♂	26	1.3	1.2	....	Negative	Well child
227	14 yr.	♀	33	1.4	1.1	....	Negative	Well child
228	3 yr.	♂	30	1.8	...	....	Negative	Well child
229	6 yr.	♂	30	2.6	1.3	....	Negative	Well child
230	8 yr.	♂	27	2.0	...	....	Negative	Well child
231	12 yr.	♀	31	2.1	1.0	....	Negative	Well child
232	10 yr.	♀	32.1	2.0	1.3	....	Negative	Well child
233	14 yr.	♀	28	...	1.5	....	Negative	G. C. vaginitis
234	11 yr.	♀	34	2.0	1.2	....	....	G. C. vaginitis
235	1 mo.	♂	34	1.5	...	....	....	G. C. vaginitis
236	5 mo.	♀	28	1.4	1.2	....	....	G. C. vaginitis
237	4 yr.	♀	30	3.2	...	....	Negative	Epilepsy
238	9 yr.	♂	35	1.6	...	....	Alb., tr.	Epilepsy
239	......	♂	36	2.6	...	....	Negative	Epilepsy
240	8 yr.	♀	30	2.2	...	....	Negative	Epilepsy
241	7 yr.	♀	21	1.6	...	....	Negative	Epilepsy
242	9 yr.	♂	27	2.2	...	....	Negative	Petit mal
243	8 yr.	♂	27	3.9	...	....	Negative	Epilepsy
244	7 yr.	♂	32	2.6	...	....	Negative	Epilepsy
245	5 yr.	♂	30	...	...	....	Negative	Epilepsy
246	10 yr.	♂	35	3.1	...	....	Negative	Epilepsy
247	9 yr.	♀	27.2	3.2	1.5	....	Negative	Epilepsy
248	1 yr.	♂	31	2.0	1.1	....	Negative	Petit mal
249	5 yr.	♀	21	1.6	...	....	Negative	Epilepsy
250	4 mo.	♂	26	3.6	...	....	Negative	Malnutrition, D.
251	8 mo.		16	0.7	...	....	Alb., tr.	Malnutrition
252	8 mo.	♂	30	1.2	...	....	Negative	Malnutrition
253	10 mo.	♀	23	0.8	...	....	Negative	Malnutrition
254	9 yr.	♀	37	3.0	...	....	Alb., tr.	Dementia praecox
255	11 yr.	♀	30	2.5	...	....	Negative	Tumor of spinal cord
256	1 mo.	♀	25	1.5	1.0	....	....	Foundling
257	......	♂	25	1.9	...	....	Negative	Constipation
258	7 yr.	♂	35	3.5	1.5	....	Negative	Constipation
259	10 yr.	♂	30	2.8	...	....	Negative	Constipation
260	4 yr.	♀	30	2.3	1.2	....	Negative	Little's disease
261	7 yr.	♂	..	1.5	...	....	Negative	Idiot
262	8 mo.	♂	31	1.5	1.1	....	....	Mongol.
263	6 mo.	♂	29	...	...	....	Alb., tr.	Idiot
264	14 mo.	♂	24	2.1	1.1	....	Negative	Idiocy
265	8 yr.	♂	30	2.5	...	....	....	Scurvy (idiot)
266	7 yr.	♀	28	...	...	....	Negative	Cretin
267	6 yr.	♂	33	2.0	0.8	....	Negative	Cretin
268	1 yr.	♀	29	2.5	...	....	Negative	Cretin
269	8 yr.	♀	31.5	1.0	...	....	Negative	Cretin
270	10 yr.	♀	32.7	2.0	1.0	....	Negative	Cretin
271	4 yr.	♂	30	2.1	1.1	....	Negative	Cretin
272	13 yr.	♀	30	1.0	...	....	Negative	Cretin
273	4 mo.	♀	37	3.3	...	....	....	Hydrocephalus
274	1 yr.	♂	31	2.3	...	....	Negative	Birth injury
275	9 yr.	♂	27	2.4	...	....	Negative	Hemophilia
276	1 mo.	♂	27	2.4	...	....	Negative	Anemia
277	7 yr.	♂	30	2.1	...	....	Negative	Anemia
278	6 yr.	♀	30	2.4	...	....	Negative	Anemia
279	7 yr.	♀	26	2.5	...	....	Alb., tr.; W.B.C., 1+	Anemia
280	10 yr.	♂	21	2.0	...	....	Negative	Undiagnosed
281	6 yr.	♀	28	2.0	...	....	Negative	Spleen
282	3 yr.	♂	25	1.9	...	....	Negative	Spleen
283	8 yr.	♂	28	2.5	1.2	....	Negative	Obs. for nephritis
284	3 yr.	♂	20	2.5	...	....	Negative	Obs. for nephritis
285	6 yr.	♂	24	2.8	...	....	Negative	Obs. for nephritis
286	11 yr.	♀	26	2.2	1.0	....	Negative	Obs.
287	7 yr.	♂	33	1.8	...	....	Negative	Obs.
288	8 yr.	♀	30	2.6	...	....	Negative	Obs.
289	12 yr.	♀	31	2.6	1.0	....	Negative	Obs.
290	4 yr.	♂	20	1.8	1.1	....	Negative	Obs.
291	4 yr.	♂	30	1.0	...	....	Negative	Obs.
292	11 yr.	♀	29	1.7	1.2	....	Negative	Obs.
293	1 yr.	♂	29	2.6	...	....	Negative	Purpura
294	1 yr.	♂	26	3.8	...	....	Negative	Purpura
295	6 yr.	♂	30	2.4	1.2	....	Alb., tr.	Purpura
296	1 yr.	♂	21	1.4	1.4	....	Negative	Tetany
297	13 mo.	♂	25	1.6	1.0	....	Negative	Tetany

* In this column, ♀ indicates female; ♂, male.

The answer to the entire question with which we are concerned is found in Chart 1, in which the range of nitrogenous constituents found in the examination of blood from ninety-one normal children is compared to that of 217 children with infections of all kinds.

Definite evidence of retention of nonprotein nitrogen, uric acid and creatinin is shown in about one half the cases of infections. There seemed to be no constant individual relationship between the increase of uric acid and of nonprotein nitrogen, but, considering all infections, high uric acid was noted in a greater number of cases than was a high nonprotein nitrogen.

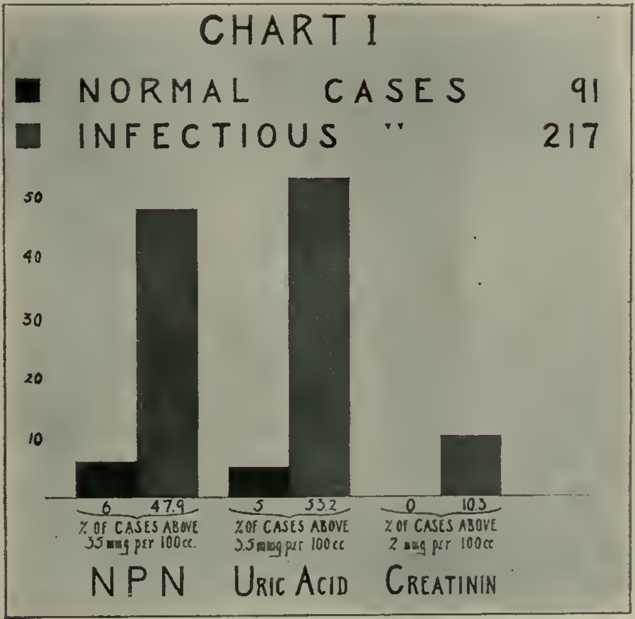

Chart 1.—Comparison of blood chemistry of ninety-one normal children and that of 217 children presenting infections.

INCIDENCE OF RETENTION IN VARIOUS INFECTIONS

Pneumonia.—In seventy cases of pneumonia, the averages and percentage of figures above high normal point plainly toward a definite effect on kidney function in this disease, more pronounced in children over 2 years of age than in those under.

Bronchitis.—Of five cases examined, one showed an increase of nonprotein nitrogen, and two an increase in uric acid.

Tuberculosis (Pulmonary, Glandular and Miliary).—These twelve cases show the same general increase as cases presenting other infec-

Table 2.—*Two Hundred and Seventeen Infections*

Case	Age	Sex*	Non-protein Nitrogen	Urea Nitrogen	Uric Acid	Creatinin	Retention, per Cent.	Urine	Diagnosis
1	3 yr.	♀	42	14	1.8	1.3	....	Alb., h. tr.; pus, 2+	Pyelitis, Imp.
2	11 yr.	♀	40	..	4.0	...	....	Alb., 2+; pus, 44.4	Pyelitis, Imp.
3	3 yr.	♀	22	..	2.2	...	....	Pus, 38%	Pyelitis, Imp.
4	4 yr.	♀	21	..	3.9	...	....	Alb., 2+; sugar, +; pus, 2+	Pyelitis, Imp.
5	......	♀	49	..	5.7	...	1-30, 2-30 (1/26/23)	Alb., tr.; pus, 2+	Pyelitis, Imp.
6	7 yr.	♀	40.8	..	3.0	...	33	Alb., neg.; pus, +	Pyelitis, Imp.
7	8 yr.	♂	50	..	4.0	1.4	....	Alb., h. cloud; pus, 4+	Pyelitis, rectal vesicular fistula, C.
8	1½ yr.	♀	22.6	..	5.6	...	....	Alb., cloud; pus, 2+	Pyelitis, rickets, O. M. P. A., Imp.
9	2½ mo.	♀	76	..	10.0	3.0	31.1	Alb., 3+; pus, 3+	Pyelitis, D.
10	......	..	37.5	..	2.4	...	....	Alb., neg.; pus, 1+	Pyelitis, Imp.
11	3 yr.	♀	29	..	2.1	1.0	1-20, 2-10	Alb., neg.; few W.B.C	Pyelitis, chronic, Imp.
12	3 yr.	♂	30	..	3.6	...	3-44	Alb., tr.; casts; W.B.C.; R.B.C,	Tonsillitis, C.
13	7 yr.	♀	35.2	..	5.6	...	40	Alb., +	Tonsillitis, C.
14	9 yr.	♀	31	..	7.2	...	....	Alb., ft. tr.; W.B.C.	Tonsillitis, C.
15	3 yr.	♂	30	..	4.5	...	....	Alb., 2+	Tonsillitis, C.
16	6 yr.	♂	36	..	5.6	1.8	1, 2-46	Negative	Tonsillitis, C.
17	8 yr.	♂	45	..	3.0	...	....	....	Tonsillitis, C.
18	5 yr.	♀	39	..	3.2	...	....	Alb., tr.; W.B.C.	Tonsillitis, C.
19	8 yr.	♀	21	..	4.4	...	....	Alb., 2+; W.B.C.; casts	Tonsillitis, C.
20	6 yr.	♀	28	..	7.0	...	....	Not tested	Tonsillitis, C.
21	6 yr.	♂	41	..	2.4	...	....	....	Tonsillitis, C.
22	4 yr.	♀	28	..	5.0	...	....	Negative	Tonsillitis, C.
23	4 yr.	♂	45	..	6.1	2.0	....	Alb., tr.; W. B. C.	Tonsillitis, C.
24	6 mo.	♀	24	..	1.3	1.2	....	Not tested	Peritonsillar abscess, C.
25	7 yr.	♀	29	..	5.8	...	....	Negative	Tonsillitis, C.
26	3 yr.	♂	22	..	4.0	...	....	Negative	Tonsillitis, C.
27	3 yr.	♂	39	..	4.8	...	1-40	Alb., h. cloud; W.B.C.; casts	Tonsillitis, C.
28	9 yr.	♂	46	..	4.2	1.4	....	Negative	Encephalitis, Imp.
29	3 yr.	♂	34	..	2.1	1.3	....	Negative	Encephalitis, D.
30	8 yr.	♂	39	..	8.0	...	....	Alb., 3+; casts	Encephalitis, Imp.
31	8 yr.	♂	40	..	8.0	...	....	Negative	Encephalitis, Imp.
32	2 yr.	♂	36	..	2.2	...	....	Alb., tr.; W.B.C.	Encephalitis, Imp.
33	11 yr.	♀	46	..	2.7	1.1	....	Neg., 43.1	Encephalitis, Imp.
34	11 yr.	♀	34	..	1.3	1.2	....	Alb., ft. tr.	Encephalitis, Imp.
35	4 yr.	♂	37	..	4.0	1.2	....	Negative	Encephalitis, Imp.
36	7 yr.	♂	36	..	3.5	...	....	Not tested	Encephalitis, Imp.
37	7 yr.	♂	55	..	5.3	...	....	Not tested	Encephalitis, bronchopneumonia, D.
38	6 yr.	♂	31.5	..	3.0	...	....	Negative	Encephalitis, D.
39	3 yr.	♂	30	..	4.5	...	....	Alb., 2+; casts 0	Encephalitis, Imp.
40	10 yr.	♂	35	..	1.8	1.5	....	Negative	Chorea, Imp.
41	10 yr.	♂	28	..	1.4	1.2	....	Negative	Chorea, Imp.
42	11 yr.	♀	27	..	1.7	1.3	....	....	Chorea, Imp.
43	9 yr.	♀	23	..	1.4	1.2	....	Negative	Chorea, Imp.
44	7 yr.	♀	28	..	1.6	1.3	....	Negative	Chorea, Imp.
45	9 yr.	♀	32	..	2.1	1.4	....	Negative	Chorea, Imp.
46	7 yr.	♀	..	..	2.0	1.1	....	Negative	Chorea, Imp.
47	11 yr.	..	37	..	3.9	1.4	....	Negative	Chorea, Imp.
48	9 yr.	♂	35	..	3.6	...	....	Negative	Chorea, Imp.
49	12 yr.	♀	43	..	2.6	...	.....	Negative	Chorea, cardiac, Imp.
50	8 yr.	♀	27	..	3.6	...	....	Negative	Chorea, Imp.
51	9 yr.	♀	27	..	3.33	2.0	....	Negative	Chorea, con. syphilis, Imp.

* In this column, ♀ indicates female; ♂, male.

TABLE 2.—*Two Hundred and Seventeen Infections—(Continued)*

Case	Age	Sex*	Non-protein Nitrogen	Uric Acid	Creatinin	Retention, per Cent.	Urine	Diagnosis
52	8 yr.	♂	38	3.26	1.7	....	Negative	Chorea, Imp.
53	8 yr.	♂	31	3.20	...	....	Negative	Chorea, Imp.
54	8 yr.	♂	40	3.63	...	....	Negative	Chorea, Imp.
55	10 yr.	..	35	2.20	1.3	....	Negative	Chorea, Imp.
56	6 yr.	..	28	2.90	1.5	....	Negative	Chorea, Imp.
57	11 yr.	♀	34	2.0	1.2	....	Negative	Chorea, Imp.
58	8 yr.	..	35	1.5	1.1	....	....	Chorea, Imp.
59	10 yr.	♂	48	5.	...	....	Negative	Chorea, Imp
60	7 yr.	♂	34.5	3.7	1.2	35, 25	Negative	Chorea, Imp.
61	12 yr.	♂	31.2	2.5	...	....	Negative	Chorea, Imp.
62	6 yr.	♀	42.6	2.1	...	....	Negative	Chorea, Imp.
63	10 yr.	♀	35	1.3	...	....	....	Chorea, Imp.
64	9 yr.	♂	30	2.4	...	....	Negative	Chorea, cardiac, Imp.
65	6 yr.	♀	40	3.6	...	....	....	Chorea, Imp.
66	9 yr.	♀	46	3.7	...	....	Negative	Chorea, Imp.
67	9 yr.	♂	31	3.0	...	....	Negative	Chorea, Imp.
68	12 yr.	♀	30	3.2	...	....	Alb., tr.; W.B.C.	Chorea, Imp.
69	10 yr.	♂	39	2.5	...	....	....	Chorea, Imp.
70	10 yr.	♀	36.6	3.0	...	....	Negative	Chorea, Imp.
71	12 yr.	♂	50	3.0	...	....	....	Chorea, cardiac, Imp.
72	11 yr.	♂	25	4.6	...	....	Negative	Chorea, Imp.
73	9 yr.	♀	29.5	4.8	...	....	Negative	Chorea, Imp.
74	......	♀	35.2	2.5	...	....	Negative	Chorea, Imp.
75	11 yr.	♂	46	2.9	...	....	Negative	Chorea, Imp.
76	11 yr.	♂	43.8	2.3	...	....	Negative	Chorea, cardiac, Imp.
77	5 yr.	♀	26.3	2.1	...	....	Negative	Chorea, cardiac, Imp.
78	5 yr.	♂	36.6	2.8	...	....	Negative	Chorea, Imp.
79	8 yr.	♀	40	2.7	...	....	Alb., tr.	Chorea, Imp.
80	10 yr.	♀	41	4.2	...	....	Negative	Chorea, cardiac, Imp.
81	7 yr.	♀	44	3.0	...	....	Negative	Chorea, cardiac, Imp.
82	8 yr.	♀	35.2	7.2	...	....	Alb., tr.	Chorea, cardiac, Imp.
83	9 yr.	♂	37.5	3.5	...	....	Negative	Chorea, Imp.
84	2 yr.	♂	40	3.6	...	....	Alb., 2+; sug. 2+	Tuberculous meningitis, D.
85	3 yr.	♂	102	6.6	...	....	....	Tuberculous meningitis, D.
86	2 yr.	♀	38	3.8	1.7	....	Alb., 2+	Tuberculous meningitis, D.
87	7 yr.	♂	43	3.0	1.4	. ..	Alb., tr.	Tuberculous meningitis, D.
88	1 yr.	♂	76	...	...	....	Negative	Tuberculous meningitis, D.
89	2 yr.	♀	91	5.0	2.1	....	Not tested	Tuberculous meningitis, D.
90	12 yr.	♂	46	2.7	1.4	....	Alb., casts	Tuberculous meningitis, D.
91	2 yr.	♂	44	6.2	...	....	Alb.; W.B.C., 42.8%	Tuberculous meningitis, D.
92	......	♂	85	9.4	1.7	....	Not tested	Tuberculous meningitis, D.
93	1 yr.	♀	35	2.0	...	....	Negative	Tuberculous meningitis, D.
94	3 yr.	♂	32	3.7	...	2 hr., 45	Negative	Acute bronchitis, C.
95	5 yr.	♂	19	3.0	...	....	Negative	Acute bronchitis, C.
96	6 yr.	♂	30	1.0	...	....	Negative	Acute bronchitis, rickets, C.
97	1 yr.	♂	41.1	4.0	...	....	Negative	O. M. P. A., anemia, C.
98	......	♂	27	3.4	...	....	....	Chronic bronchitis, C.
99	11 yr.	♂	39	4.0	1.4	....	?	Pulmonary tuberculosis (?)
100	9 mo.	♂	33	4.0	...	....	?	Pulmonary tuberculosis, D.
101	10 yr.	♀	41	3.2	1.4	1-30, 2-25	Alb., ft. tr.	Pulmonary tubc., Imp.
102	4 yr.	♀	30	2.5	...	....	Negative	Pul. tbc., N. A. O. R., Imp.
103	3 yr.	♀	44	3.0	1.4	....	Negative	Pulmonary tubc., Imp.
104	6 yr.	♂	22	3.6	...	41	Negative	Pulmonary tuberculosis, U.
105	10 yr.	♀	26	1.5	...	29.6	Negative	Pulmonary tuberculosis, U.
106	2 yr.	♀	20	4.0	...	....	Negative	Tbc. cerv. nodes phlyct. conjunc., Imp.
107	18 mo.	♀	24	7.4	1.1	....	Negative	Tbc, cerv. nodes phlyct. conjunc., A. O. R.
108	1 yr.	♂	31	4.0	...	....	Negative ?	Tbc. cerv. nodes, Imp.
109	3 yr.	♂	36	4.0	...	....	Negative	Miliary tuberculosis, D.
110	9 mo.	♂	38	4.5	...	....	Alb., 5%; W.B.C.	Miliary tuberculosis, D.
111	1 yr.	♂	27	1.7	1.2	....	Negative	Rickets
112	6 mo.	♀	27	1.0	1.3	....	....	Rickets, tetany
113	6 mo.	♂	22	1.3	1.2	....	....	Rickets, tetany
114	5 mo.	♀	26	...	...	....	W.B.C.	Rickets, tetany
115	4 mo.	♂	29	3.5	1.3	....	....	Rickets
116	8 mo.	♂	30	2.5	...	....	Negative	Rickets
117	10 mo.	♂	20	2.3	...	....	Negative	Rickets
118	2 yr.	♂	25	2.7	...	....	....	Rickets
119	4 mo.	♂	31.5	2.0	1.2	....	Negative	Rickets
120	6 mo.	♀	19	3.2	...	....	Negative	Rickets
121	1 yr.	♂	20	2.0	...	....	Negative	Rickets
122	2 yr.	♂	20	2.0	...	....	Negative	Congen. deformity of hands and feet
123	4 yr.	♂	27	2.6	...	....	Negative	Mental deficiency
124	7 yr.	♂	26.7	1.0	1.3	....	Negative	Chondrodystrophy

* In this column, ♀ indicates female; ♂, male.

TABLE 2.—*Two Hundred and Seventeen Infections—(Continued)*

Case	Age	Sex*	Non-protein Nitrogen	Uric Acid	Creatinin	Retention, per Cent.	Urine	Diagnosis
125	12 yr.	♂	30	2.0	...	....	Negative	Club foot
126	8 yr.	♂	39	2.0	1.4	....	Negative	Fractured humerus I week postoperative
127	6 yr.	♂	33	2.0	1.0	....	Negative	Contracture
128	3 mo.	♂	23.5	3.0	...	....	Negative	Diet regulation
129	13 yr.	♂	30	3.0	1.0	....	Negative	Chlorosis
130	2 yr.	♂	35	1.3	...	....	....	Diphtheria, C.
131	2 yr.	♂	37	7.2	2.0	....	....	Diphtheria, cerv. abscess, Imp.
132	4 yr.	♂	32	1.4	1.4	....	....	Diphtheria, Imp.
133	9 mo.	♀	31	3.0	1.7	....	Not tested	Whooping cough, Imp.
134	6 mo.	♀	32	1.7	1.4	....	....	Measles. C.
135	4 yr.	♂	34	4.1	...	....	....	Poliomyelitis, Imp.
136	8 mo.	♂	40	3.0	...	....	Alb.. W.B.C.	Furunculosis, Imp.
137	2 mo.	♂	24	1.0	...	....	Alb., +; sug., +	Furunculosis, O. M. P. A., Imp.
138	3 mo.	♀	35	2.3	...	....	Not tested	Furunculosis, C.
139	7 mo.	♂	30	6.5	2.7	....	Alb., +; sug., 2+; pus, +; casts	Eczema furunculosis, AOR
140	9 yr.	♀	34	3.1	...	....	Not tested	Typhoid, C.
141	10 yr.	♂	28	0.7	...	....	Negative ?	Typhoid, C.
142	2 yr.	♀	33	3.7	...	....	Alb., +	Typhoid, C.
143	18 mo.	♀	18	5.0	...	....	Alb., +; W.B.C.	Ac. cholangitis, Imp.
144	4 yr.	♀	31	4.6	...	....	Negative, 41%	Ac. cholangitis, Imp.
145	8 yr.	♂	30	6.0	...	....	....	Ac. cholangitis, Imp.
146	8 yr.	♂	34	1.2	1.0	....	Negative	Ac. rheum. fever, Imp.
147	4 yr.	♀	25	2.6	...	....	Negative	Ac. rheum. fever, C.
148	2 yr.	♂	49.8	2.0	1.4	....	Negative	Eczema, Imp.
149	1 yr.	♂	42	8.2	...	....	37%	Pemphigus, D.
150	4 yr.	♀	28	6.8	...	....	Alb., tr.	Epidem. meningitis, C.
151	4 yr.	♂	29.5	4.0	...	....	Negative	Chronic epidem. meningitis, hydro., D.
152	9 yr.	♀	30	5.4	...	1-20, 2-5	Alb., N.; pus, +	Stomatitis, C.
153	10 yr.	♂	40	3.6	1.4	....	Alb., 2+; casts	Septicemia, Imp.
154	3 yr.	♂	27	5.3	1.2	2-55	....	Scarlet fever, Imp.
155	1½ yr.	♂	40	3.0	...	....	....	Chr. meningitis, Imp.
156	2 yr.	♂	22	2.1	...	....	Negative	Lob. pn., rickets, Imp.
157	1 yr.	♂	23	2.5	1.9	1-45	Alb., ft. tr.; W.B.C.	Lob. pn., rickets, Imp.
158	10 mo.	♀	30.4	5.4	...	....	Negative	Lob. pn., anemia, C.
159	6 mo.	♀	30	7.0	...	....	Not tested	Lob. pn., microceph., D.
160	18 mo.	♀	22	4.1	2.7	....	Alb., 2+	Lob. pn., O. M. P. A., pyelitis, rickets, D.
161	8 mo.	♂	30	2.5	...	....	Alb., 2+; W.B.C.	Lob. pn., D. M. P. A., C.
162	17 mo.	♀	26	3.3	...	....	....	Lob. pn., O. M. P. A., C.
163	17 mo.	♂	20	2.3	...	....	Negative	Lob. pn., O. M. P. A., C.
164	2 yr.	♂	32	1.8	1.4	....	Negative	Lob. pn., O. M. P. A., C.
165	5 mo.	♂	30	5.4	...	....	Negative	Lob. pn., O. M. P. A., D.
166	15 mo.	♂	33	2.6	1.3	....	....	Lob. pn., effusion, Imp.
167	2 yr.	♂	53	2.4	1.6	....	Negative	Lob. pn., mastoid, D.
168	15 mo.	♂	39	1.8	...	....	Alb., +; casts	Lob. pn., O. M. P. A., D.
169	14 mo.	♀	38	1.3	1.5	....	Negative	Lob. pn., O. M. P. A., D.
170	1 yr.	♀	26.1	4.0	...	....	Alb., tr.; W.B.C.	Br. pn., rickets, D.
171	1 yr.	♀	40.8	5.3	...	....	Not tested	Br. pn., rickets. D.
172	1 yr.	♀	22	2.4	...	....	Negative	Br. pn., O. M. P. A., C.
173	6 mo.	♂	41	4.0	...	....	Alb., h. cloud; W.B.C.; casts	Br. pn., O. M. P. A., C.
174	1 yr.	♀	38.7	4.0	...	....	Not tested	Br. pn., W. C., D.
175	3 mo.	♂	35.2	4.0	1.0	....	Not tested	Br. pn., D.
176	9 mo.	♂	43	5.5	...	....	....	Br. pn., necropsy showed cloudy swelling
177	16 mo.	♂	52.5	6.8	...	....	Negative	Br. pn., scurvy, con. heart condition, A. O. R.
178	9 mo.	♂	15	5.3	...	....	Alb., N.; sug., 2+; mx., N.	Br. pn., D.
179	2 yr.	♂	34	1.1	...	....	Negative	Br. pn., O. M. P. A., W. C., D.
180	6 mo.	♂	37	11.4	...	....	Alb., tr.	Br. pn., O. M. P. A., D.
181	7 mo.	♂	26	1.8	...	....	....	Br. pn., O. M. P. A., D.
182	1 yr.	♂	27	1.4	1.2	....	Negative	Br. pn., O. M. P. A., D.
183	9 mo.	♀	20	2.3	...	....	Negative	Br. pn., O. M. P. A., Imp.
184	2 yr.	♀	29	1.9	...	....	Negative	Br. pn., rickets, A. O. R.
185	1½ yr.	♀	30	3.0	1.6	....	Negative	Flu., br. pn., D.
186	9 yr.	♂	26.6	3.0	...	1-15, 2-35	Negative	Lob. pn., C.
187	8 yr.	♂	36	5.6	1.2	1-25, 2	W.B.C.; Grm.; Alb., N.; casts	Lob. pn., C.

* In this column, ♀ indicates female; ♂, male.

TABLE 2.—*Two Hundred and Seventeen Infections—(Continued)*

Case	Age	Sex*	Non-protein Nitrogen	Uric Acid	Creatinin	Retention, per Cent.	Urine	Diagnosis
188	7 yr.	♂	29	3.6	...	1, 2-35	Negative	Lob. pn., C.
189	9 yr.	♀	38	2.5	...	....	Alb., N.; W.B.C., +	Lob. pn., C.
190	3 yr.	♂	60	5.2	1.8	Anuria 24 hr.	Alb., h. tr.; casts	Lob. pn., O. M. P. A., Imp.
191	6 yr.	♂	40	5.2	1.4	2-42	Alb., h. cloud; mx., neg.	Lob. pn., C.
192	3 yr.	♂	39	4.8	1.2	1-40, 2	Alb., h. cloud; W.B.C.; gram casts	Lob. pn., C.
193	11 yr.	♂	33.5	3.4	...	1-25, 2-15	Negative	Lobar pn., C.
194	8 yr.	♀	27	4.3	1.5	1-55, 2-10	Negative	Lobar pn., C.
195	6 yr.	♀	37	4.0	1.5	1-60, 2-25	Alb., cloud; neg. gram casts	Lobar pn., C.
196	3 yr.	♀	25.2	7.2	...	....	Alb., N.; W.B.C.	Lobar pn., D.
197	3 yr.	♂	22	1.0	...	....	Alb., 2+; casts;	Lobar pn., C.
198	3 yr.	♂	28	1.4	1.2	....	Alb., 1+	Lobar pn., C.
199	3 yr.	♂	44	1.3	1.4	....	....	Lobar pn.
200	6 yr.	♀	25	6.3	...	....	Negative	Lobar pn., C.
201	7 yr.	♀	46	4.7	1.7	45	Alb., tr.; casts; W.B.C.	Lobar pn., C.
202	3 yr.	♂	26	4.5	1.4	40	Alb., tr.	Lobar pn., C.
203	5 yr.	♂	46	5.2	1.6	....	....	Lobar pn., D.
204	9 yr	♂	30	1.7	1.3	35	Negative	Lobar pn., C.
205	8 yr.	♀	42	5.2	1.6	....	....	Lobar pn., D.
206	......	..	27	4.7	2.2	....	Alb., tr.; W.B.C.	Lobar pn., O. M. P. A., C.
207	2 yr.	♂	22	4.2	...	....	Negative	Lobar pn., I.
208	6 yr.	♂	34	5.7	1.6	....	Negative	
209	8 yr.	♀	37	3.6	1.7	1-15, 2-12	....	Lobar pn , I.
210	7 yr.	♂	30	4.0	...	1-33, 2-17	....	Lobar pn., I.
211	3 yr.	♀	44	1.2	1.5	....	....	Lobar pn., C.
212	8 yr.	♀	48	3.3	1.5	45	....	Lobar pn., I.
213	4 yr.	♂	35	4.4	...	....	Neg., 42.6%	Lobar pn., C.
214	......	..	28	1.7	1.9	....	Negative	Lobar pn., O. M. P. A , I.
215	4 yr.	♂	46	3.2	...	....	Alb., tr.	Lobar pn., I.
216	7 yr.	♀	48	6.0	1.7	....	Not tested	Lobar pn., D.
217	6 yr.	♀	40	4.5	2.1	....	Alb., tr.	Lobar diph., C.
218	10 yr.	♀	28	3.4	...	....	Negative	Cardiac lobar pn., G. C. vaginitis, D.
219	5 yr.	♂	20.6	4.8	...	2-5	Alb., N.; W.B.C., 2+	Br. pn., D.
220	8 yr.	♀	28	3.8	...	30	Alb., 1+	Br. pn., ac. rheum., F.
221	2 yr.	♀	33	1.0	1.5	....	....	Br. pn., measles, C.
222	4 yr.	♀	28	5.6	...	....	Neg., 32%	Br. pn., O. M. P. A., I.
223	3 yr.	♀	35	3.0	1.5	....	Alb., N.; W.B.C.	Br. pn., O. M. P. A., 1.
224	8 yr.	♂	27.1	5.0	1.2	....	Alb., tr.; W.B.C.	Lobar pn., C.
225	2½ yr.	♀	31	7.0	...	....	Alb., tr.; W.B.C.	Br. pn., D.
298	12 yr.	♂	25.5	3.1	1.1	1-30, 2-20	....	Contracture fingers, 24 hr. postoperative
299	12 yr.	♂	34.5	2.0	1.2	1-40, 2-20	....	Contracture, 7 days postop.
300	11 yr.	♀	30	5.3	1.2	1, 2-50	....	Contracture fingers, 24 hr. postoperative
301	11 yr.	♀	30	2.8	1.1	1-20,2-22.5	....	Contracture, 1 wk. postop.
302	6 yr.	♂	31	3.0	1.1	1-50, 2-5	....	Web fingers, 24 hr. postop.
303	6 yr.	♂	33	2.4	1.0	....	....	Web fingers, 1 wk. postop.
304	10 yr.	♂	29	4.4	1.2	1-10, 2-5	Negative	Ing. hernia, 24 hr. postop.
305	10 yr.	♂	41.6	3.4	1.2	....	....	Ing. hernia, 1 wk. postop.
306	7 yr.	♂	30	3.8	1.0	1-40, 2-20	....	Ing. hernia, 24 hr. postop.
307	7 yr.	♂	33	2.3	1.1	....	....	Ing. hernia, 1 wk. postop.
308	3 yr.	♂	37.5	8.8	1.6	1-25, 2-15	Negative	Ing. hernia, 24 hr. postop.
309	3 yr.	♂	28.5	2.3	1.1	....	....	Ing. hernia, 1 wk. postop.
310	11 yr.	♂	33.3	2.6	1.0	1-5, 2-30	....	Ing. hernia, 24 hr. postop.
311	11 yr.	♂	37.5	2.0	1.0	1-20,2-12.5	....	Ing. hernia, 1 wk. postop.
312	4½ yr.	♂	35.2	6.1	1.5	....	....	Ing. hernia, 24 hr. postop.
313	4½ yr.	♂	21	1.0	1.0	....	....	Ing. hernia, 1 wk. postop.
314	7 mo.	♂	26	5.0	1.8	1-50, 2-30	....	Ing. hernia, 24 hr. postop.
315	7 mo.	♂	20.7	3.0	1.0	....	....	Ing. hernia, 1 wk. postop.
316	10 yr.	♂	42.6	5.2	...	1-15, 2-25	....	Ing. hernia, 48 hr. postop.
317	10 yr.	♂	26.6	2.7	...	....	....	Ing. hernia, 1 wk. postop.
318	6 yr.	♀	37.5	3.7	1.5	1-50, 2-10	....	Skin graft, 24 hr. postop.
319	6 yr.	♀	30.8	2.2	1.0	1-50, 2-10	....	Skin graft, 1 wk. postop.
320	5 wk.	♀	54.5	8.0	1.4	....	....	Gastrotomy, 24 hr. postop.
321	5 wk.	♀	30	2.0	1.0	....	....	Gastrotomy, 8 days postop.

* In this column, ♀ indicates female; ♂, male.

tions, the uric acid being increased in a higher percentage of cases than is the nonprotein nitrogen.

Tuberculous Meningitis.—In the ten cases, the retention is more pronounced in these cases, as one would expect in so severe an infection. This is one of the groups in which the nonprotein nitrogen is increased in a higher percentage of cases than is the uric acid.

Epidemic (Lethargic) Encephalitis.—In the twelve cases, there is a greater number of high nonprotein nitrogen values than of high uric acid values.

Tonsillitis.—In the sixteen cases in this group, an increase in nonprotein nitrogen in 43 per cent. of the cases and of uric acid in 75 per cent. of the cases shows very well the selective action of the kidney. Tonsillitis is accepted as being of especial etiologic importance, or at least as a frequent precedent condition in nephritis, and the type of retention corresponds to that of nephritis.

Pyelitis.—In the eleven cases, the patients who were sick showed retention and those that were not definitely sick had no retention. The degree of retention followed closely the clinical evidences of the severity of the infection.

Chorea.—In forty-three cases of chorea, the nonprotein nitrogen was up in 58.1 per cent. of the number, while the uric acid was high in only 30.2 per cent. Chorea is considered by some as an infection, though it usually runs an afebrile course. The rise in the nonprotein nitrogen level may not be a retention, for the urinary findings are consistently negative, and phenolsulphonephthalein tests made in chorea cases in the last few years have always shown a normal output.

Miscellaneous Infections.—This group of twenty-six cases shows in general the same changes that the other cases of acute infections show.

Surgical Conditions, Noninfectious.—Blood was taken within twenty-four hours after operation in selected clean cases.[16] These patients showed about the same degree of retention as those having acute infections. Phenolsulphonephthalein tests made in ten cases at the same time blood was taken showed a low output (below 50) in four, or 40 per cent. It is interesting to see what effect a combination of shock and anesthesia can have on kidney function. Blood taken one week after operation gave normal findings in practically all of the cases.

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[16] These cases became available for test through the kindness of Dr. Carl Burdick, Children's Surgical Division, Bellevue Hospital.

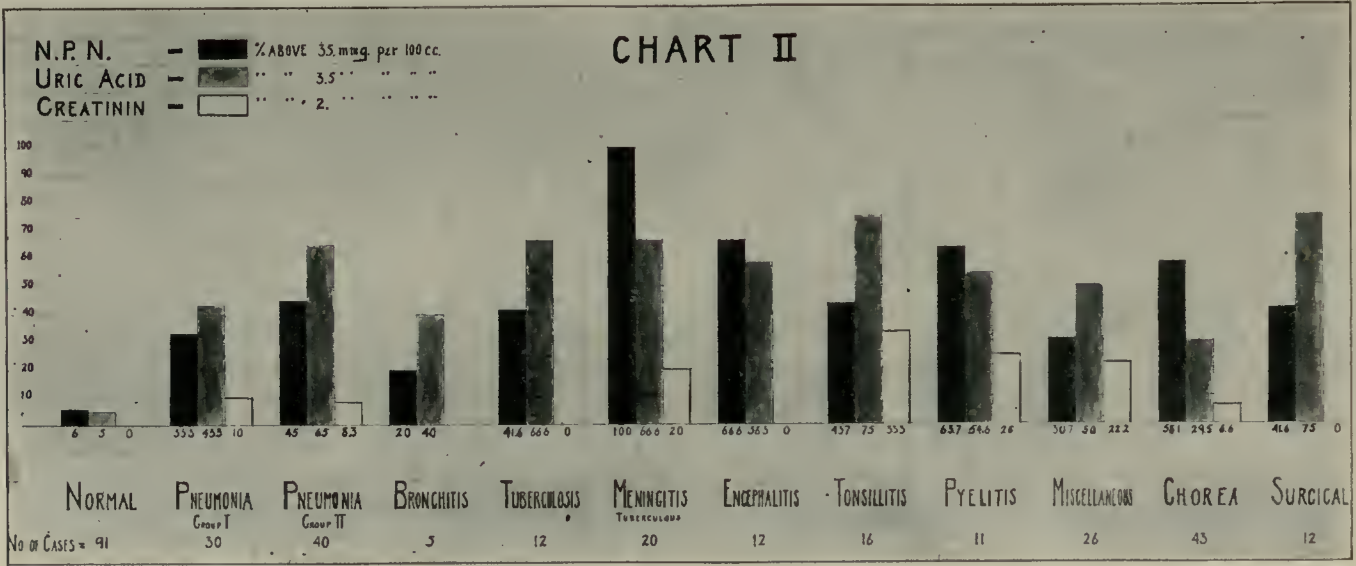

Chart 2.—Percentage increase of nonprotein nitrogen, uric acid and creatinin in 217 infections grouped according to disease.

COMMENT

Mosenthal[17] has shown that in adults the picture of functional impairment found in severe acute nephritis is produced by other conditions, such as pyelitis, cystitis, anemia and diabetes.

The treatment of any of these conditions would certainly be modified if we were aware of the degree to which the kidney function was being hampered by the primary condition, or, conversely, how much such an unrecognized kidney deficiency might be hindering progress.

We do not mean to say that every acute or chronic infection or affection must be subjected to an annoying and expensive series of functional tests, but it should be borne in mind that additional trouble from poor kidney elimination is a possible source of complication, and attention to the kidney function is as important as attention to the action of the intestinal tract. The figures shown in Chart 1 are a basis for this attitude, as there was definite increase in the nitrogen constituents of the blood in about 50 per cent. This could not be attributed to blood concentration because all the hematocrit readings taken were within normal limits, most of them being at about 35 per cent., and none over 45 per cent.

It is also probable that in infection there is toxic destruction of protein; but, normally, the kidney could take care of any increase in waste products from this source. Coleman and Du Bois demonstrated a toxic destruction of protein in typhoid. We have blood chemistry findings in the cases of three children with this disease. They are all well within normal limits except one with a uric acid of 3.7.

It is difficult to decide whether these evidences of nitrogen retention are to be interpreted as due to functional disturbance simply or to actual early nephritis.

Examination of the urine revealed signs of kidney irritation in only half the cases. Less confidence is felt in this evidence because, unfortunately, routine ward analyses were depended on, and therefore there exists certain inaccuracy and incompleteness common to every such procedure.

We were unable to demonstrate any constant relation between blood chemistry on the one hand and urinary analysis or functional tests on the other. Blood retention was associated with normal urine: low phenolsulphonephthalein excretion, with normal blood chemistry; albumin, casts and white blood cells (in urine) with normal blood chemistry and phenolsulphonephthalein excretion.

Comparable to this lack of consistency in these functional tests of kidney competency are the variations found in retention of all elements of nonprotein nitrogen, and in a seemingly selective action on certain of them.

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[17] Mosenthal, H. O., and Richards, A. E.: Interpretation of a Positive Nitrogen Balance in Nephritis, Arch. Int. Med. **17**:329 (Feb.) 1916.

Myers [18] and others have long contended that, in the early stages of renal insufficiency, the uric acid is the first nitrogen constituent to be retained, and that in the absence of gout a rise in uric acid in the blood signifies a mild impairment of kidney function; or, in other words, uric acid accumulation precedes and exceeds that of nonprotein nitrogen in the early stages of nephritis.

Folin [19] notes that in gout it is the only substance increased, and asks whether "this is to be interpreted in terms of a highly selective activity and correspondingly selective deterioration of the kidneys, or does it mean that uric acid is more difficult to excrete than any other waste product, a possibility suggested by the high normal levels and by excessive variation in uric acid content of blood of normal persons." In nephritis leading to uremia and in advanced cases of nitrogen retention, there is no constant relationship between increase in nonprotein nitrogen and uric acid, and the latter seldom shows a greater percentage increase than does nonprotein nitrogen. On the contrary, the uric acid accumulation is usually less pronounced.

Foster [20] thinks that, in the early stages, the kidney is intolerant of certain substances, and as the disease progresses, the kidney becomes more tolerant.

Our figures seem to support the view that increase of uric acid is significant of actual early kidney impairment rather than simply dysfunction. Retention does not progress equally as regards the various constituents of nonprotein nitrogen.

Taking the infections as a whole, the difference is not marked, 48 per cent. showing an increase in nonprotein nitrogen, as against 53 per cent. showing an increase in uric acid. But tonsillitis, pneumonia, tuberculosis and the miscellaneous infections show a greater number with high uric acid than with high nonprotein nitrogen retention, the relation being about 60 to 40 per cent.

Estimation of disturbed relation between fluid intake and output is as worthy of observation in any acute condition as is the routine observation of the intestinal function. From it, evidence of faulty fluid elimination may be obtained before actual signs of retention have appeared; and with it in mind, a better estimate of slight early variations in the chemical composition of the blood is possible.

Foster [20] emphasizes the importance of this consideration of fluid balance and retention in the blood. He states that the amount of nitrogen excretion in the urine bears a relation to the volume of urine, and gives experimental confirmation of a well established clinical doctrine; namely, that these cases of chronic nephritis with nitrogen retention require much water in order to eliminate the nitrogenous waste, because the diseased kidney can excrete only at a low level of concentration of urea.

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[18] Myers, U. C.; Fine, M. S., and Lough, W. G.: Blood in Nephritis, Arch. Int. Med. **17**:570 (April) 1916.

[19] Folin, O.: Physiol. Rev. **2**:460 (July) 1922.

[20] Foster, Harvey Lectures, 1921.

Pepper[21] stresses the influence of oliguria on nitrogen excretion and blood retention, and believes that nitrogen retention may depend entirely on failure of water elimination without impairment of the urea excreting function of the kidney.

There were forty-three deaths in the series of infections. Of these, 83.7 per cent. showed a retention of one or more of the nitrogenous waste products, as opposed to 50 per cent. of the total infections investigated.

CONCLUSIONS

1. In a series of 217 acute infections (including twelve postoperative noninfections), retention of nitrogenous waste products was shown in about one half of the cases.

2. This retention is thought to be due to simple impairment or depression of kidney function, though in some groups of cases the possibility of nephritis could not be ruled out.

3. Of the three nitrogenous waste products studied, nonprotein nitrogen, uric acid and creatinin, the uric acid was above normal in a greater number of cases than were nonprotein nitrogen and creatinin. This selective retention is shown especially well in the group of twenty-six miscellaneous infections, seventy cases of pneumonia and sixteen cases of tonsillitis. The type and degree of retention in these groups makes one think that possibly we are dealing with early but definite acute nephritis.

4. In some textbooks, no mention is made of kidney function, although many pages are devoted to diet and general hygiene in the treatment of acute infections. Others state that evidences of serious renal impairment are seldom found in early life.

It is clear from the evidence that, in many cases of acute infection, there is definite impairment of kidney function which may not be evident clinically. Certain of these cases may go on to actual nephritis. Emphasis is therefore laid on the necessity for more careful consideration of the kidney in all acute infections and its routine protection from all unnecessary strain.

In some cases, prevention of impending kidney breakdown will thus be provided for; in others, treatment directed at the kidney will be instituted at an early rather than at a late date.

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[21] Pepper, O. H. P.: Am. J. Med. Sc. **165**:81 (Jan.) 1923.

REFLEXES OF THE NEW-BORN *

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The study of the reflexes of the new-born has not led until now to exact conclusions as to their mode of action or pathognomonic importance. The various researches on the reflexes, and especially on the most important of them, the plantar and knee reflexes, often give contradictory results as to their mode of action and frequency. Therefore, I think that a summary of results which I obtained from a careful examination of new-born children in the first week of life will be of interest.

The imperfect development of the nervous system in the new-born, due to the embryonal type of ganglionic cells, especially the pyramidal ones, and to the myelinization deficiency, especially in the fibers of the brain, alters all nervous functions; and exact knowledge of these variations from the normal is necessary for the differentiation of physiologic from pathologic phenomena. The younger the child the more important this knowledge is.

As there are no important and clear clinical signs of the nervous organic alterations in the first period of life, we are compelled to weigh carefully the least change in nervous reactions, especially those reflexes which are usually tested. The differences, sometimes very marked, that one encounters among the results reported by various authors who have studied the reflexes in the new-born are due, I think, to some fault in the methods of observation and the interpretation.

Examination of the reflexes in the child, and much more in the new-born infant, presents great technical difficulty, which must be overcome with much patience and requires numerous and careful observations. The physiologic muscular hypertonia of the new-born; the incessant moving about, and the difficulty in limiting the intensity and extension of a stimulus hinder both production of the reflexes and their interpretation, besides causing marked variability in reactions under the same conditions. Therefore, it is easy to note, in several successive tests of a reflex, variations in the result, which compel one to repeat the test several times, in order to reach precise definite conclusions.

Besides, one must bear in mind that after the same reflex has been tested repeatedly in the new-born, a kind of muscular fatigue or an

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adaptation to the stimulus results, so that, in protracting the observation, one, at last, excites a reflex which is entirely different from the first ones in quality and intensity.

Another factor in the variation in the reflex is the means employed for stimulation. Intense and brief stimulation, with rough stinging objects can produce a reaction quite different from that obtained by gentle stimulation with smooth objects. A vigorous stimulation elicits not only the reflex which is sought, but also a series of muscular contractions which are extraneous to those peculiar to the reflex and which interfere with its interpretation.

These various conditions make research difficult, and largely explain the differences in results obtained by observers.

My researches were made on eighty-eight new-born infants in the first week of life, and have been carried out, for the most part, during the first two days after birth.

The examinations have been made repeatedly under varying conditions; with the baby sleeping, waking, weeping, resting, etc.; never tiring the baby, and examining one or two reflexes at a time. The final conclusions as to the behavior of each reflex are the synthesis of various examinations carried out under different circumstances.

All new-born infants observed were constitutionally sound and had no disease. In analyzing the results, I have considered the various etiologic factors: age, sex, weight, etc., but as I have noted no relation between them and the behavior of the reflexes, consideration of each factor singly is not worth while. It may be noted, in a general way, that an inverse relation exists between the tendinous and cutaneous reflexes according to body weight; that is, the greater the weight and development of the baby, the more vigorous the cutaneous reflexes and the weaker the tendinous reflexes, and vice versa. This observation, however, has some exceptions.

A CONSIDERATION OF THE VARIOUS REFLEXES

In presenting the results obtained, it seems necessary to consider each reflex separately.

Cutaneous Reflexes.—The first and most important is the plantar reflex. Babinski,[1] on attributing the phenomenon he described to alterations of the pyramidal tract, deduced, as a corollary of this conception, that the phenomenon should be physiologic in the new-born, because of the insufficient myelinization of that tract at birth. In fact, his own researches and those of others later confirmed this deduction experimentally.

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[1] Babinski: Semaine méd., 1898.

But latterly some observers (Gindiceandrea,[2] Finizio [3]) have noted that by stimulating the sole of the new-born, one produces flexion, as occurs normally in the adult, instead of extension of the toes. Therefore, while some observers think that, in healthy new-born children in the first week, the plantar reflex consists in the dorsal flexion of the toes, others believe that plantar flexion is the rule. Engster,[4] in 232 new-born children, found dorsal flexion constantly, except in two cases in which there was plantar flexion, and in eight in which the reflex was not elicited. Léri,[5] in 166 new-born infants, found, as a rule, the dorsal flexion and, exceptionally, the plantar.

On the contrary, Finizio,[3] in fifty new-born infants, found that the plantar reflex was absent in 5 per cent., was undecided in 10 per cent., and consisted in extension in 15 per cent., and in flexion in 70 per cent.

The results of my examinations led me to a conclusion analogous to Feldman's; [6] that is, the usual response of the plantar reflex is the plantar flexion of the toes. For reflex stimulation, I employed the dorsal surface of the little finger nail, passed swiftly, thinking such a stimulus the best on account of its uniformity. In the reflex interpretation, many times, the classification of the type was not easy, because the toe movement was very undecided because of the alternation of flexion and extension in response to successive stimuli.

When one stimulates the sole, the first responsive movement generally accentuates the position of the toes at the instant of stimulation. This position, normally, consists in extension of the great toe and flexion of the other toes, but at times the four toes extend and the great toe is flexed, or all toes extend or are flexed together.

These movements are not constant, but extremely variable, so that, several times successively, each response may contradict the one preceding.

In seeking the normal reflex for a given new-born, I have not considered the first seventy elicited, but the type proved most frequent. I thus noted that there is but little difference between the percentage of reflexes showing flexion and those showing extension, having found the former in 57 per cent. and the latter in 43 per cent. On no occasion was there complete failure of the reflex; on the contrary, reflexes in the new-born are very pronounced.

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2. Gindiceandrea: Soc. Lancisiana d. osp. di Roma, 1899.
3. Finizio: La Pediatria, August, 1900.
4. Engster: Wien. klin. Wchnschr. **18**:567, 1905.
5. Léri, M. A.: Gaz. d. mal. inf. **5**:277, 1903.
6. Feldman, W. M.: Nature of Plantar Reflex in Early Life and Causes of Its Variation. Am. J. Dis. Child. **23**:406 (Jan.) 1922.

Response to the plantar stimulation is given not only by toe movements, but by flexion movements of the whole foot; and the stronger the stimulation, the more intense the response. These movements, the result of special reflexes, have no clinical value in the new-born.

The plantar reflex, always present, is much attenuated in premature infants and in new-born infants who are under weight.

Abdominal Reflex.—This is elicited with difficulty, and must be tested during sleep or while the baby is nursing, is hardly perceptible in 77 per cent., rather intense in 16 per cent., and absent in 7 per cent. It is seldom elicited in well-developed and well-nourished new-born infants.

Cremasteric Reflex.—This by some authors (Griffith)[7] has been constantly found at birth; by others (Finizio[3]), it is noted only exceptionally in the new-born (2 per cent.). I found it present in 92 per cent., the intensity varying with the descent of the testicles.

Corneal and Pharyngeal Reflexes.—These reflexes are present in all new-born infants and are very vigorous.

Tendinous Reflexes,—In order to provoke these reflexes, I employed percussion with a small hammer. I tested various reflexes, but the doubtful results I obtained led me to consider only the knee reflex, because it is difficult to differentiate the movements due to tendon contraction from that caused by the hammer. I have divided the knee reflex into three types according to liveliness, and I found that it is normal in 20.4 per cent.; exaggerated in 54.5 per cent.; much exaggerated in 21.6 per cent., and absent in 3.5 per cent. I have further noted a difference of intensity in the two reflexes (16 per cent.), and even the presence of the reflex in one knee and the absence in the other (5.6 per cent.). This condition is commonly found in premature infants.

Pupillary Reflexes.—There is great difficulty in classifying these reflexes, because of their variety. I found in 17 per cent. obstinately myotic pupils, with barely perceptible oscillation toward the light. In 20.5 per cent., there were enlarged pupils, with slow movements. The reflex as it occurs in 62.5 per cent. is a series of alternations which begin with a contraction provoked by a luminous stimulus, followed by dilatation. Thus there develops a movement of pendulum type which gradually slackens, then recommences at a new stimulus, or sometimes without it. Several times the dilatation of the pupils was not in relation to the quantity of light reaching the eye, nor were the movements in relation to the variations of light.

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7. Griffith, J. P. C.: The Diseases of Infants and Children, Philadelphia, W. B. Saunders Company **1**:65, 1919.

From these results, one can deduce that the physiologic significance of reflexes in the new-born varies greatly from that of reflexes in the adult. The first difference consists in their greater liveliness, a result of lack of development of the nervous system and cerebral inhibition, not on physiologic hypertonicity. This activity is observed only in the first tests of the tendinous reflexes, diminishing if repeated stimulation causes the muscular fatigue. For cutaneous reflexes, the initial activity does not change.

More remarkable are differences in mode of response, especially for plantar and pupillary reflexes, so that while they have great diagnostic value in the adult, they have none in the new-born.

The variableness is more evident in the cutaneous and pupillary than in the tendinous reflexes, which behave very much as in the adult. As to the presence or absence of reflexes, one can say that they present no variations from those of the adult. With patience, waiting for a right moment, one may succeed in eliciting all reflexes in the new-born. From my observation, I have concluded that almost all reflexes are present at birth, and only exceptionally some one of them does not appear until sometime during the first months. This is in opposition to the observations of Bychowsky,[8] who says that many reflexes make their appearance during the first months of life.

CONCLUSION

The great variability of reflexes in the new-born, whose modification and intensity vary widely, makes it impossible to attach to them the pathognomonic importance they have in the adult.

It is difficult, unless there are great deviations, to judge whether the intensity of a given reflex is strengthened or weakened, if it reveals pathologic nervous alterations, when even in normal conditions such remarkable differences exist. It may be that besides modification and intensity, the presence or absence of reflexes, in the new-born, may have pathognomonic importance. Since all reflexes, cutaneous and tendinous, are present at birth, the absence of one or more of them only can give some indication of nervous injury.

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[8] Bychowsky: Ztschr. f. Nervenh. **34,** January, 1923.

EXOPHTHALMIC GOITER IN CHILDHOOD WITH SOME UNUSUAL MANIFESTATIONS *

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During the past few years, unusual interest has been aroused in the study of thyroid conditions. Perhaps the most important stimulus has been the more general application of basal metabolism determinations. The improved operative technic and the more extensive use of roentgen-ray therapy have also played an important rôle.

The occurrence of three cases of exophthalmic goiter in children in private practice suggested a study of this condition as manifested in childhood. Two of these cases were observed also on the pediatric service at Mount Sinai Hospital.

Exophthalmic goiter was known many centuries ago. The ancient Romans realized that slaves afflicted with this condition were unfit for strenuous work. It was not recognized, however, that exophthalmos was a symptom of a disease until Flajani's work in 1780. Perry, in 1786, noted the same fact. The description of the disease as we know it was given by Graves in 1835 and by von Basedow in 1843. The first case in a child was recorded by Henoch-Romberg[1] in 1851.

INCIDENCE, AGE AND SEX

Although exophthalmic goiter is rare in childhood, in the course of years a large number of cases have been reported. In a series of 1,512 cases at the Mayo Clinic, there were five children under 10 years of age (0.3 per cent.). Klein[2] mentions a series of 3,477 cases, which included 184 in children under 15 years (5 per cent.). Barret,[3] who made a most exhaustive study of the condition in childhood, believes the ratio of children to adults is 1:50. He collected thirty-nine cases in children reported in the literature before 1901. The youngest was 2½ years. There were three cases in children less than 5 years of age; eleven between 5 and 10 years, and twenty-five from 10 to 15 years. The youngest patient in the Mayo Clinic series was 4 years. A case cited by Ochsner and Thompson[4] may have been congenital. A woman of 35 years developed exophthalmic goiter during pregnancy. A premature birth occurred at seven and one half months. Five weeks after birth, the infant's eyes became abnormally prominent. No men-

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[1] Henoch-Romberg: Klin. Wahrnehm and Beobacth., Berlin, 1851, p. 178.

[2] Klein, S.: Arch. Pediat. **39**:786 (Dec.) 1922.

[3] Barret, G.: Paris Theses, 1901.

[4] Ochsner and Thompson: The Surgery and Pathology of the Thyroid and Parathyroid Glands, p. 192, 1910.

tion was made, however, of the thyroid or the pulse rate in the original report by Schmauch. During the first year of life, the condition is extremely rare. The ages of our patients when symptoms of the disease first became manifest were 4, 5, and 7 years, respectively.

Sex distribution shows a definite preponderance of females. In Barret's review of thirty-nine cases in children, there were twenty-eight girls and eleven boys. In the series of cases mentioned by Klein, 84 per cent. of the cases were in girls. All three cases of our group are in girls.

ETIOLOGY

The etiology of exophthalmic goiter has been the subject of considerable experimentation, speculation and dispute. One group of workers, Filelines, Walburton and Tedeschi, thought the disease had a bulbar origin. They sectioned the restiform bodies and produced the symptoms of hyperthyroidism in animals. Trousseau, Charcot, Gerhardt and Sattler believed the condition was a neurosis of the whole vegetative nervous system. Nutkine and Blum thought there was a thyroid insufficiency and a consequent insufficient detoxication of the body. Basedow believed the condition due to a poisoning of the blood by thyroid products. Hart and Bircher suggested a thymic origin.

Moebius believed the disease was produced by a hypersecretion of the thyroid gland. This opinion has been widely held for a long time. The recent studies of exophthalmic goiter by Kessel, Lieb and Hyman,[5] however, seem to refute this view. They point out that this condition may exist in the presence of a normal or colloid thyroid and that hyperplasia of the gland may coexist with myxedema. In no instance has it been possible to develop artificially, by the administration of large doses of thyroid extract to man or animal, a typical case. They believe the condition to be "(1) a clinical collection of sympathomimetic symptoms (tachycardia, exophthalmos, sweating, asthenia, polyrrhea, etc.) associated with (2) metabolic upset (elevated basal metabolism) and usually accompanied by (3) hyperplasia of the thyroid gland." The sympathomimetic symptoms may be developed by stimulation of the thoracicolumbar division of the involuntary nervous system. The ultimate cause of the disease, then, must act primarily or secondarily through the involuntary nervous system.

HEREDITY

Heredity has played an important rôle in a large number of reported cases. Dejerine[6] believed that exophthalmic goiter occurs in neuropathic families. Dubrenil-Chambardel[7] reported a family in which the grandmother, mother and two daughters of 4 and 7 years, all had exophthalmic goiter. Lonques and Lermoyez[8] described a family with seven cases of exophthalmic goiter. Climenko recorded the history of a family in which the mother, two daughters and two grandchildren, girls of 6 and 10 years, all had the disease. In a report by Frantz,[9] a girl of 9 years and her mother were afflicted with the condition. In our group of three cases, careful inquiry into the family histories did not reveal any hereditary tendencies.

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[5] 5. Kessel, Leo; Lieb, C. C., and Hyman, H. T.: Exophthalmic Goiter and Involuntary Nervous System, J. A. M. A. **79**:1099 (Sept. 30) 1922; **79**:1213 (Oct. 7) 1922.

[6] 6. Dejerine: Thesè d'argrey, p. 157, 1886.

SYPHILIS

Syphilis was thought to be the underlying factor in several cases. Gauches and Salin[10] record a case in which hereditary syphilis manifested itself in the form of polyglandular hyperthyroidism. Hazen[11] cites the case of a girl with secondary syphilis who developed enlargement of the thyroid with symptoms of hyperthyroidism. Rost[12] reported a case of exophthalmic goiter in a girl of 12 years with marked toxic symptoms, whose blood Wassermann reaction was four plus. She showed definite improvement under antisyphilitic treatment. In none of our cases was there any history of syphilis. The Wassermann test was negative in two of the cases. In one, it was not made.

PATHOLOGY

The structure of the thyroid gland and its pathology has been clearly described by Marine.[13] Uniform enlargement of the thyroid may be produced by a hyperplastic or a colloid gland. In the former, the epithelium is higher and the walls of the alveoli may be thrown up into plications. There is increased blood vessel supply and at times round-cell infiltration of the stroma. The colloid is diminished.

In the colloid gland, there is a formation of large amounts of colloid material which stretch the alveolar spaces and produce a flattened epithelium. There is marked thickening of the walls of the blood vessels. Transitional forms are found in which there may be colloid, in a hyperplastic gland; and vice versa. Discrete enlargements of the gland may be produced by adenomas or cysts. An adenoma may have the same structure as normal, colloid or hyperplastic thyroid tissue.

Thyroxin, an iodin-containing substance, has been isolated by Kendall,[14] as the specific secretion of the thyroid gland.

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[7] Dubrenil-Chambardel: Province Med., p. 262, 1907.

[8] Lonques and Lermoyez: Rev. Neurol. **35**:20 (Jan.) 1919.

[9] Frantz, M. H.: New York M. J. **113**:275 (Feb. 12) 1921.

[10] Gauches and Salin: Bull. Soc. franç. de dermat. et syph. **23**:62, 1912.

[11] Hazen, H. H.: Am. J. Syphilis **3**:205 (April) 1919.

[12] Rost, William: Arch. Pediat. **39**:458 (July) 1922.

[13] Marine, David: J. Lab. & Clin. Med. **3**:40 (Oct.) 1917.

[14] Kendall, E. C.: J. Biol. Chem. **40**:265 (Dec.) 1919.

One of our patients, the child of 5 years, was operated on by Dr. Crile, and portions of the right and left lobes of the thyroid were removed. There was considerable colloid present, with slight hyperplasia of the parenchyma. No tumors were found.

SYMPTOMATOLOGY

The cardial symptoms of exophthalmic goiter are tachycardia, exophthalmos and enlarged thyroid gland. The most important diagnostic test is an increased basal metabolism. Barret, from his study of thirty-nine cases in childhood, believes that tachycardia is the first important symptom to develop. The average pulse rate ranged between 100 and 120. In six cases, the rate was 150 or over. In our cases, the pulse rate was in direct relation to the severity of the condition, the mildest case having the lowest rate. In the three cases, the range of the pulse rates before treatment was: first case, from 100 to 110; second case, from 120 to 130; third case, from 160 to 180.

The exophthalmos is usually less marked in children than in adults, but its presence is generally definitely observed. In Barret's report, it was absent in only eight of the thirty-nine cases. In our experience, it was distinctly present in all three cases, and the degree of exophthalmos was in direct relation to the severity of the condition, the case of the most rapid pulse rate and the highest basal metabolism having the most marked prominence of the eyes. Graefe's and Stellwag's signs were present in all our cases. Moebius' sign was elicited in one of the three cases.

Enlargement of the thyroid gland was noted in all our cases. A distinct bruit over the gland was heard in two instances.

The basal metabolism test has proved to be the most important guide in diagnosis as well as in the determination of the severity of the disease. In 182 cases of exophthalmic goiter in adults, before any treatment, Sandiford[15] found an average metabolic rate of + 51 per cent. In children afflicted with a disease manifested by considerable excitability, it is often difficult to perform the test, as complete muscular relaxation is essential. We were fortunate in obtaining the perfect cooperation of our patients. The tests were made by Dr. Herman Lande of Mount Sinai Hospital. The Tissot method of indirect calorimetry was employed. Benedict and Talbot's standards, based on weight, were used. The results in the three cases before treatment were: first case, + 12 per cent.; second case, + 20 per cent.; third case, + 52 per cent. Clinically, the degree of severity of the symptoms and signs corresponded with the degree of elevation of the metabolic rate.

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[15] Sandiford, Irene: Endocrinology **4**, No. 1.

The minor symptoms of exophthalmic goiter are tremor, excitability, polyphagia, diarrhea and hyperhidrosis. Osler [16] believed tremor to be one of the cardinal symptoms, but in childhood it has not been frequently observed. It was noted in only four of Barret's series of thirty-nine reported cases. In a number of later reports, its absence was noted. In two of our cases, a fine tremor of the hands was observed. Hyperhidrosis was present in all three cases.

Alertness and irritability were present in all our cases. The mentality of the children was above the average. In the three cases, the height of our patients was noticeably above normal, in one case 2 inches (5 cm.), in the other cases, about 4 inches (10 cm.). The weight in two cases was normal; in one case, with the markedly elevated basal metabolism, 5 pounds (2.27 kg.) below normal. In the latter, too, constant marked hunger and diarrhea were annoying symptoms of the disease.

An unusual manifestation was the development of severe recurrent attacks of ketosis in this case. Major [17] has recently called attention to this condition following roentgen-ray treatment of the thyroid and partial thyroidectomy. Crile [18] believes that in fatal cases of exophthalmic goiter the usual cause of death is acidosis, and that so-called postoperative hyperthyroidism is mainly acute acidosis. We have not found any records of this complication, however, in cases before treatment was instituted. The first time we had the opportunity of seeing our case was during such an attack.

We found the child of 4 years in deep coma. The room was filled with the fruity odor of the ketone bodies. The respiration rate was 60 per minute; the pulse rate, 180; the temperature, 103 F. There was no cyanosis. There were marked convulsive twitchings of all the extremities. The child could not be aroused. She seemed to be in extremis. The urine showed much acetone and diacetic acid. We immediately gave a hypodermoclysis of 250 c.c. of 5 per cent. glucose solution, repeating it in half an hour. Within an hour, the improvement was remarkable. The patient became perfectly conscious, the respirations and pulse rate diminished considerably and she was able to take fluids by mouth. Her condition was normal in twenty-four hours.

It was after this attack that the symptoms and signs of exophthalmic goiter became evident. The patient has had three similar attacks since then, several months apart, each time responding perfectly to the administration of glucose solution by hypodermoclysis. We are now giving her glucose in her diet regularly, as we do in every severe case of acidosis, from 1 to 2 drams (3.75 to 7.5 cm.) a day, and during the past six months she has had no attacks. The exophthalmic goiter, however, has grown progressively worse. The mother has refused operative interference. During one of the attacks of ketosis, the child was in the hospital and a complete blood examination was made. There were no abnormal findings except the diminution of the carbon dioxid content, which was 34.7 per cent. by volume. The blood sugar was 0.15 per cent.

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16. Osler, William: Principles and Practice of Medicine, p. 878, 1912.

17. Major, R. H.: Acidosis in Hyperthyroidism, J. A. M. A. **80**:83 (Jan. 13) 1923.

18. Crile, G. W.: Ann. Surg., Sept. 25, 1915.

Blood counts were made in all our cases, but did not show the lymphocytosis frequently found.

TREATMENT

The treatment of exophthalmic goiter has passed through a number of stages. Jacobi,[19] who reported four cases in children between the ages of 9 and 13 years in 1879, employed arsenious acid, atropin and extract of ergot as the most successful drugs. A number of other reports included the use of digitalis, iron and salicylate of soda. Electricity was employed in some of the earlier cases. Thyroid and thymus extracts were used.

With the advent of modern surgery great strides were made in the management of thyroid conditions. The preoperative care, the operative technic and the postoperative vigilance have been perfected to a remarkable degree. A report from the Mayo Clinic showed that in 1,093 operations for exophthalmic goiter there were eleven deaths, or 1.005 per cent. Of these, 523 were partial thyroidectomies, with a mortality of 0.96 per cent.

Sandiford has demonstrated the fall in the basal metabolic rate after operation in cases of exophthalmic goiter.

The roentgen ray has been employed, with some very favorable results. The most recent work along this line, by Means and Holmes,[20] showed that in forty-four recent cases of exophthalmic goiter treated by roentgen ray twenty-eight patients were improved. Of these, twelve were apparently cured and sixteen improved but not entirely well. In no instance was a case made worse. In the favorable cases, there was a rapid fall in pulse rate (from an average of 115 to 89) and basal metabolism (from an average of 55 per cent. to + 21 per cent.

Radium emanations have been used by Terry in the treatment of exophthalmic goiter, mainly in preparation for thyroidectomy. Of sixteen patients, two were cured by radium alone; ten were well after resection of the thyroid, and four died after operation.

As so many good results were reported from various therapeutic procedures, Kessel, Lieb and Lande,[21] in their recent studies of this condition, were prompted to determine whether exophthalmic goiter did not show a tendency to spontaneous recovery. They studied the natural course of the disease in fifty cases under hygienic conditions and the least possible psychic disturbance. No specific treatment was employed. Bed rest was given from six to ten weeks. They state that the tendency to recovery in these patients was "astounding." Forty-one, or 82 per cent., of the patients were "socially or economically restored." There was a marked decrease in the basal metabolic rate. An absolute restoration to a perfectly normal condition, as far as their observations up to the time of writing went, rarely occurred.

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[19] Jacobi, A.: New York M. Rec., July 5, 1879.

[20] Means, J. H., and Holmes, G. W.: Further Observations on the Roentgen-Ray Treatment of Toxic Goiter, Arch. Int. Med. **31**:303 (March) 1923.

[21] Kessel, Leo; Hyman, H. T., and Lande, Herman: A Study of Fifty Consecutive Cases of Exophthalmic Goiter, Arch. Int. Med. **31**:433 (March) 1923.

In our group of three children, one with a case of moderate severity, with a basal metabolism of + 20 per cent. and a pulse rate of 120, was operated on by Dr. Crile about three months ago. A partial thyroidectomy was performed. She was seen by us recently, and the marked improvement in her condition was evident. Her mother reported considerable improvement in nervousness and irritability. The eyes were much less prominent, though a slight exophthalmos persisted. The pulse rate had decreased to 102. No tremor was elicited. A nocturnal enuresis which she had previously had disappeared. The basal metabolism was normal.

A second case of moderate severity has been observed at intervals for the past two years. As far as we know, no specific treatment has been employed. The patient has had occasional periods of bed rest, but has attended school most of the time. Her basal metabolism has remained about the same, + 16 per cent. The pulse rate varies between 110 and 120.

In the most toxic case of the group, with a basal metabolism of + 52 per cent. and pulse rate ranging between 160 and 180, the patient has had a long period of rest treatment. She has been in bed at intervals for periods from two to four weeks. Her condition has not improved. The exophthalmos is more marked. The pulse rate ranges between 150 and 160. The thyroid gland has increased in size. The attacks of ketosis, however, have not recurred recently. The mother has refused consent for operation. Roentgen-ray treatment is under consideration.

In the light of all the recent evidence regarding treatment, it seems the most rational procedure to institute first a regimen of strict physical and psychical rest for six to ten weeks. If the patient shows no improvement, a short period of roentgen-ray therapy should be tried. Thyroidectomy should be performed if there is no response to the roentgen ray. On account of the toxic action on the heart in the severe cases, it is safer not to wait too long before operation.

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EXPERIMENTAL OBSERVATIONS ON THE ETIOLOGY OF CHOREA *

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Numerous investigators have made cultures of the throat, tonsils, blood and spinal fluid of patients with chorea. Collins [1] isolated from the blood of a patient with severe chorea gram-positive cocci which grew in pairs, or in chains of from four to six. La Fetra [2] reported the finding of *Streptococcus viridans* in the blood of two patients with chorea. Camisa [3] isolated a diplostreptococcus from the blood of six of nine patients with chorea minor. The blood of twenty-one patients was cultured by Quigley,[4] and in nine of these he found small cocci arranged in pairs and in short chains. Positive results on culturing the spinal fluid were obtained in thirteen of twenty-one cases, and the organisms in eight of the thirteen resembled those found in the blood. Poynton and Paine [5] obtained a diplococcus from the spinal fluid of two patients dying with rheumatic fever associated with symptoms of chorea. With one of these strains, arthritis, endocarditis and pericarditis were produced in rabbits. These authors were able to demonstrate microscopically the diplococci around the pial vessels in the two fatal cases. From the blood, brain, tissues and heart valves from a fatal case of chorea following arthritis, Westphal, Wassermann and Malkoff [6] obtained a streptococcus with which arthritis could be produced in rabbits. Richards [7] obtained *Streptococcus viridans* from the blood in fourteen of 104 cases of arthritis, and he was able to demonstrate the presence of the same organism in four of fifty-four joint cultures. The same organism was found in cultures of the blood in five of sixteen cases of chorea, and it was also demonstrated in cultures from the

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* From the Division of Experimental Bacteriology, The Mayo Foundation.

1. Collins, J. R.: Rheumatism and Chorea, Brit. M. J. **1**:220-221, 1913.

2. La Fetra, L. E., discussion of Strauss, I.: Present Conception of Chorea, Arch. Pediat. **32**:135-136, 1915.

3. Camisa, G.: Bakteriologische Untersuchung des Blutes der Chorea minor Kranken, Centralbl. f. Bakteriol. **57**:99-107, 1910-1911.

4. Quigley, W. J.: Observation on the Bacteriology of Chorea, J. Infect. Dis. **22**:198-204 (March) 1918.

5. Poynton, F. J., and Paine, A.: Some Investigations on the Nervous Manifestations of Acute Rheumatism, Lancet **2**:1760-1765, 1905.

6. Westphal, Wassermann and Malkoff: Ueber den infectiösen Charakter und den Zusammenhang von acutem Gelenkrheumatismus und Chorea, Berl. klin. Wchnschr. **34**:638-640, 1899.

7. Richards, J. H.: Bacteriologic Studies in Chronic Arthritis and Chorea, J. Bacteriol. **5**:511-525 (Sept.) 1920.

tonsils, teeth and nasal mucous membrane. The spinal fluid in nineteen cases of chorea was found sterile by Morse and Floyd,[8] but positive results were obtained in five of twenty-six cases in which cultures of the blood were made. Streptococci were demonstrated in three of the five positive cases. Dick and Rothstein[9] have reported the occurrence of choreic symptoms in a dog following the intravenous injection of a streptococcus cultured from the throat of a patient with chorea of five years' duration. Floyd[10] isolated streptococci from teeth and tonsillar crypts in seventeen of twenty cases of chorea, and was able to produce endocarditis and swelling of the joints in rabbits with these strains. The cultures of the blood in all cases were negative.

The findings at necropsy in a patient with chorea, who had had numerous attacks of rheumatism, are reported by Dana.[11] There was chronic leptomeningitis of a convexity of the brain, slight meningitis of the upper spinal cord and slight meningo-encephalitis. Microscopic examination of tissues of the superior parietal lobules revealed thickening of the pia, the result of connective tissue proliferation, without exudate or round-cell infiltration. Gram-positive diplococci were found, free and on the inner surface of the membrane, in sections stained by Weigert's method.

These bacteriologic studies, while indicating that chorea is a streptococcic disease, do not furnish convincing proof that this is so, because in only a few instances has the disease been produced experimentally with the organisms isolated. My own studies in this field have yielded results which furnish important additional proof that chorea minor is the result of a particular streptococcic infection.

EARLY OBSERVATIONS ON INTRAVENOUS INJECTION

The hypothesis that chorea might be due to a streptococcus having peculiar neurotropic properties took definite form in March, 1910, when chorea developed in a dog and a rabbit, after I had injected intravenously a streptococcus isolated from the blood during life in a fatal case of typical chorea. A low grade meningitis, most marked around the vessels in the cerebral cortex, and subcortical hemorrhages were found in both animals. The streptococcus in pure culture was recovered from the slightly turbid cerebrospinal fluid. The rabbit also had lesions of the joints, the fascial sheaths of muscles and the heart valves. Similar results were obtained on four widely separated occasions, following intravenous injection of a series of animals with cultures from tonsils during the acute stage of this disease.

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[8] Morse, J. L., and Floyd, Cleveland: A Study of the Etiology of Chorea, Am. J. Dis. Child. **12**:61-72 (July) 1916.

[9] Dick, G. F., and Rothstein, T.: A Streptococcus Producing Symptoms of Chorea in a Dog, J. A. M. A. **61**:1376 (Oct. 11) 1913.

[10] Floyd, Cleveland: A Study of Streptococci Obtained from the Mouth in Cases of Chorea, J. M. Res. **41**:467-479 (May) 1920.

[11] Dana, C. L.: On the Microbic Origin of Chorea: Report of a Case, with Autopsy, Am. J. M. Sc. **107**:3-38, 1894.

Five rabbits and two white rats of a total of thirty-five animals injected intravenously with the streptococcus isolated from the joint fluid, blood or infection-atria of patients with acute rheumatic fever developed chorea-like symptoms, besides lesions of the joints, muscles and heart.[12] The postmortem findings in the central nervous system consisted of small circumscribed meningeal hemorrhages and slightly turbid cerebrospinal fluid in the experiments of short duration; and of localized grayish nodular thickening of the pia and, microscopically, of subcortical areas of round-cell infiltration in experiments of longer duration.

Muscular movements resembling those in chorea developed occasionally following intravenous injection of cultures of streptococci from various other diseases. Choreiform movements occurred in five of a large number of animals following the injection of mass cultures from the tonsils or infected teeth of patients with chronic myositis, with or without arthritis;[13] three times with cultures of tonsils which were removed on account of their large size and because of repeated attacks of tonsillitis in persons that were well; and in one instance each following the injection of a large number of animals with mass cultures from tonsils of patients with appendicitis, ulcer of the stomach, cholecystitis, parotitis, herpes zoster and goiter. In these animals, the lesions of the central nervous system consisted of low grade meningitis and meningeal and subcortical hemorrhages (Fig. 1) in the experiments of short duration, and of perivascular and localized infiltration by round cells in the pia, and subcortical areas of necrosis and cellular infiltration (Fig. 2) in the experiments of longer duration. In the latter group of animals, the lesions of the central nervous system were believed to be more or less accidental because embolic lesions, chiefly in the organs corresponding to those affected in the patient from whom the cultures were obtained, were also found. The lesions were always due to streptococci, notwithstanding the fact that the cultures injected usually also contained a variable number of other bacteria. The streptococci isolated from the lesions or from the spinal fluid produced a greenish zone around the colonies on blood-agar plates. This was true alike in the cases of chorea, rheumatic fever and myositis, as well as in the other diseases.

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[12] Rosenow, E. C.: The Etiology of Acute Rheumatism, Articular and Muscular, J. Infect. Dis. **14**:61-80, 1914.

[13] Rosenow, E. C., and Ashby, Winifred: Focal Infection and Elective Localization in the Etiology of Myositis, Arch. Int. Med. **28**:274-311 (Sept.) 1921.

The experimental results in chorea parallel the clinical observations as regards the common occurrence of lesions in joints, muscles and endocardium in cases of chorea. The experimental results in rheumatic fever and myositis support the supposed etiologic relationship between chorea and rheumatic affections, and the rare occurrence of chorea-like symptoms in the animals injected with strains from other diseases may be regarded as representing the chorea in man which sometimes develops in the course of acute pyemia and other infections.

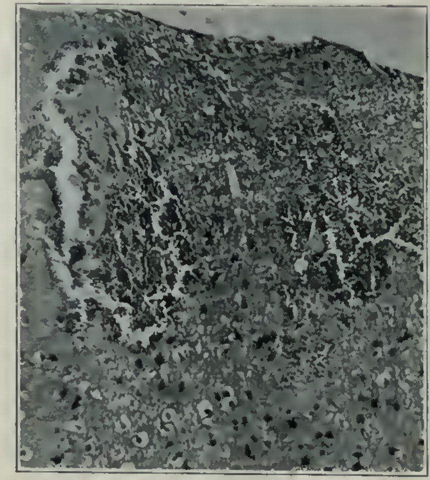

Figure 1

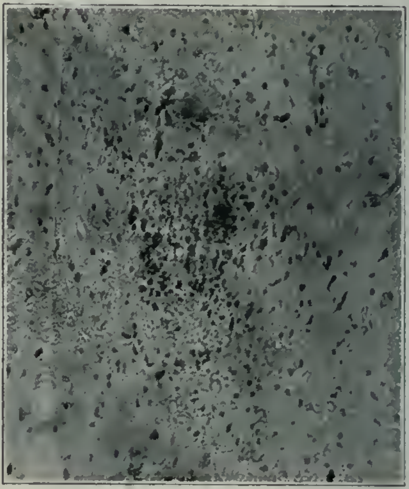

Figure 2

Fig. 1.—Localized subcortical hemorrhages in rabbit that developed choreiform movements forty-eight hours after an intravenous injection of a streptococcus from the tonsil in a case of subacute arthritis and myositis; hematoxylin and eosin; × 100.

Fig. 2.—Area of necrosis and infiltration in the subcortical region in the lower rolandic region of a rabbit that developed marked incoordinate movements of the head four days after an intravenous injection of a streptococcus from the parotid duct in a case of epidemic parotitis; hematoxylin and eosin; × 75.

With these observations in mind, I thought it worth while to study additional cases of chorea by the methods developed in connection with studies on encephalitis and allied conditions, and to compare the localizing and symptom-producing power and other properties of the streptococcus suspected of having etiologic relationship in chorea with strains of streptococci from cases of encephalitis with which various forms of encephalitis have been produced in animals.

RECENT EXPERIMENTS ON INTRACEREBRAL INOCULATION

In the experiments on encephalitis [14] and epidemic hiccup,[15] it was found that, while symptoms and lesions of the central nervous system developed in some instances following intravenous injection, intracerebral inoculation was necessary in order to measure accurately the infecting power of the bacteria suspected of having etiologic significance. Through the coöperation of Dr. Helmholz, of the Section on Pediatrics, cultures from four cases of typical chorea were obtained and observations were made following injections in animals by the intracerebral method.

REPORT OF CASES

Case 1.—A girl, aged 13 years, suffered from rheumatic pains, and swelling of the arms and legs following an attack of tonsillitis. This continued for about one month, when an attack of typical chorea developed. Animals were inoculated with cultures from this patient three months after the onset of symptoms.

Case 2.—A girl, aged 6 years, developed incoordinate movements of the mouth and the limbs several days after the extraction of a tooth. Animals were inoculated with cultures from this patient one month after the onset of symptoms. The tonsils had been removed eight days before. The incoordinate movements were severe, and examination revealed a moderate infection of the nasopharynx, many carious teeth and mitral endocarditis.

Case 3.—A girl, aged 8 years, developed incoordinate movements of the extremities from no apparent cause. The tonsils were large, and the crypts were filled with cheesy material from which pus could be expressed. The tonsils were removed five weeks later, and the patient ultimately recovered completely. About two weeks after the development of the incoordinate movements, animals were inoculated with cultures from this patient.

Case 4.—A girl, aged 12 years, developed a mild attack of chorea about ten days before our study. The characteristic organism was isolated from pus expressed from the tonsils, and from the nasopharynx. The tonsils were found to be infected, and were removed two weeks later. Several small abscesses were found, from which the streptococcus was again isolated. With rest in bed for three months, the patient completely recovered without developing demonstrable cardiac lesions.

The material cultured and injected was pus expressed from the tonsils, and the exudate from the nasopharynx obtained with wire swabs bent to the proper angle. Suspensions of each were made in 2 c.c. of sodium chlorid solution. This suspension was used for the direct injection of animals and to inoculate blood-agar plates and tall tubes of glucose-brain broth. Two rabbits were injected routinely with the suspensions, one receiving 0.1 c.c., the other 0.2 c.c. If no symptoms developed within twenty-four hours, other rabbits were injected with the primary culture in glucose-brain broth. If suggestive symptoms developed, the strains isolated from the central nervous system of the animals injected directly with the suspension were used for subsequent injections. The dose ranged from 0.1 c.c. of a 1 : 1,000 dilution to 0.2 c.c. of the undiluted glucose-brain broth culture. The number of animals injected depended largely on the results obtained. In order to rule out the possibility of a slowly growing virus, pure cultures of the streptococcus obtained from animals showing characteristic symptoms were injected after many rapidly made subcultures.

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[14] Rosenow, E. C.: Experimental Studies on the Etiology of Encephalitis: Report of Findings in One Case, J. A. M. A. **79**:443-448 (Aug. 5) 1922.

[15] Rosenow, E. C.: The Production of Spasms of the Diaphragm in Animals with a Streptococcus from Cases of Epidemic Hiccup, J. Infect. Dis. **32**:41-71 (Jan.) 1923; The Production of Spasms of the Diaphragm in Animals by Living Cultures, Filtrates, and the Dead Streptococcus from Cases of Epidemic Hiccup, J. Infect. Dis. **32**:72-94 (Jan.) 1923.

RESULTS

Seven rabbits were injected intracerebrally with cultures from Case 1, three rabbits from Case 2, two from Case 3 and nineteen rabbits and one dog from Case 4. Positive results were obtained following injections of cultures from Cases 1, 2 and 4. The two rabbits injected intracerebrally with the salt solution suspension of the culture from Case 3 remained well. Of the total of thirty-two animals injected, twenty-two (69 per cent.) developed varying degrees of ataxia; in eight (25 per cent.), the movements were definitely choreiform in type; only three developed unusual weakness of extremities; two developed marked tremor; two, markedly increased respiration, and ten, clonic contractions of the muscles of the extremities or of the neck. Only two of the twelve rabbits injected in the first animal passage developed spasms of the muscles; whereas, eight of the remaining nineteen that were injected with the streptococcus in the second animal passage developed this symptom. The ataxia or incoordinated movements were often extremely marked and the animals frequently lost their balance when made to hop. All movements disappeared during sleep. Lethargy was not observed in any of the rabbits injected with the chorea strains. In nine rabbits, no symptoms were observed. Three of these were injected directly with suspensions of nasopharyngeal swabs in sodium chlorid solution and were observed for eleven, thirty and fifty-eight days, respectively. Of the remaining six, one died in forty-eight hours, the others during the night following injection. All of the six received inoculations of the streptococcus in the second animal passage. The findings at necropsy consisted, in the main, of congestion of the vessels of the meninges and moderate or slight turbidity of the cerebrospinal fluid. Occasionally, localized hemorrhages in the pia, especially over the cerebral cortex and cerebellum, were found.

Cultures were made from the brain and the blood of twenty-seven animals. The green-producing streptococcus was isolated from the brain in twenty-four; in three, no bacteria were obtained. The blood was positive in nine of the animals and negative in eighteen.

The streptococcus which produced chorea in the animals following intracerebral inoculation of small doses was similar to the streptococcus which I isolated in 1910 and have isolated from time to time since, and which sometimes produced chorea-like symptoms on intravenous injection of large doses. The colonies produced on blood-agar were small, dry, slightly elevated and nonadherent and were surrounded by a brownish green zone. After incubation for forty-eight hours, a narrow zone of hemolysis peripheral to the greenish zone often developed. The organism produced a diffuse or slightly granular growth in glucose broth and glucose-brain broth. It was free from a capsule and was regular in size. It occurred in diplococcus forms, and the chains, of medium length, were made up of diplococci. The different strains produced acid in dextrose, lactose, saccharose and raffinose agar, but not in mannite, salicin or inulin. The fermentative power of the strain from Case 4 was tested as isolated from the brain after one, two and three animal passages in rabbits and from the teeth of the dogs three months after devitalization and after from three to fourteen subcultures. The streptococcus from chorea was only slightly virulent on intraperitoneal and intravenous injection, but more virulent than most of the encephalitic strains on intracerebral inoculation. The power to produce chorea in animals was maintained through many culture generations, as high as the twelfth, by making the subcultures from four to six times a day, and through three animal passages, but was lost rapidly on aerobic cultivation on blood-agar plates.

A monovalent serum has been prepared in a horse by repeated intravenous injections, in increasing doses, of the strain from Case 4. Each of the strains isolated from the animals following intracerebral inoculation, and which had been kept under anaerobic conditions and in dense suspensions in glycerol and sodium chlorid solutions, was agglutinated specifically by this serum. Moreover, ten of fifteen strains of a similar streptococcus isolated from myoclonic and other forms of encephalitis were also agglutinated; whereas, five control strains of streptococci isolated from sources other than chorea and encephalitis were not agglutinated by this serum. The immunization is being continued with a mixture of choreic strains. Further immunologic experiments and the findings as to the protective power and therapeutic value of the serum will be reported later.

In one experiment on a dog, localization in the brain was facilitated by injecting sterile broth intracerebrally immediately after the pulps of four teeth had been removed and a dense suspension of the culture from Case 4 had been sealed in the canals. The animal died during the night. Necropsy revealed numerous hemorrhages around the right lateral ventricle, and turbidity of the cerebrospinal fluid, due to leukocytes. A pure culture of the streptococcus introduced into the teeth was isolated from the cerebrospinal fluid.

Careful search for lesions in and around joints, muscles and heart valves was made in ten of the nineteen rabbits injected intracerebrally in Case 4. Three of the rabbits had hemorrhages and beginning endocarditis of the tricuspid or the mitral valves and lesions in the papillary muscles at the tendinous end, and four had lesions of fascial layers in muscles and around joints.

In view of these findings, four young rabbits were injected intravenously with the streptococcus from Case 4 in the second animal passage, two receiving 3 c.c. and two 5 c.c. of glucose-brain broth cultures. The rabbits were anesthetized in from three to five days. All had lesions of muscles, joints or heart valves. In one, only a few lesions of muscles developed, and in another, lesions of muscles and ligaments around the knee joints. The other two became lame in the hind extremities, and necropsy disclosed turbid joint fluid in both knee joints, and beginning embolic endocarditis. One area of endocarditis was found along the line of closure of the mitral valve, and one at the base of the chordae tendineae in the right ventricle. No symptoms referable to the nervous system developed in any of the four rabbits, but microscopic examination revealed perivascular and other infiltration, chiefly by leukocytes, and focal hemorrhages.

Localization of Chorea and Other Streptococci Following Intravenous Injection

Strains	Number of Animals Injected	Incidence of Localization in			
		Brain	Heart Valves	Joints or Muscles	Stomach
Chorea (1)	9	6	6	5	1
Epidemic encephalitis (3)	12	9	1	1	2
Epidemic hiccup (2)	8	3	0	0	0
Ulcer of stomach (5)	28	0	2	3	23

This tendency of the chorea strains to involve heart valves, joints, and muscles as well as the brain was much more marked than that of strains of streptococci from other sources. In the accompanying table, I have summarized the results in animals injected intravenously with equivalent doses of different strains, freshly isolated, and in which the examination (gross, microscopic or cultural) was sufficiently complete to determine whether or not localization occurred in brain, heart valves, joints or muscles, and stomach. The tendency of each strain to localize in these animals in structures corresponding to those commonly involved in these diseases in man is well brought out, and is in keeping with the general results of my other studies on elective localization.

ILLUSTRATIVE EXPERIMENTS FOLLOWING INTRACEREBRAL INOCULATION

Experiment 1.—Rabbit 2356, weighing 890 gm., was injected intracerebrally, March 13, 1921, with 0.1 c.c. of a 1 : 100 dilution in sodium chlorid solution of the primary culture in glucose-brain broth of the tonsil pus from Case 1. The following day, the animal was extremely shaky, tremulous and ataxic, and was scarcely able to walk on account of peculiar contractions of the muscles of the extremities. Its head was extremely wobbly. When carrot was held to its mouth, the movements of the head became violent; but after the animal had succeeded in biting off a piece, which it ate with relish, the movements became less marked; yet they recurred each time an attempt was made to bite off pieces.

March 15, 16 and 17, the animal's condition was practically unchanged. The carrot test was repeated frequently. March 18, the animal appeared quite well, was alert and sat quietly in the cage; but when it hopped, its head became extremely wobbly and was thrown backward and from side to side in a peculiar rhythmic manner. On account of similar purposeless movements of the extremities, it could scarcely maintain its balance. March 19, marked weakness had developed, but otherwise there was little change. March 21, the weakness was less marked. The animal sat quietly in the cage, with head usually retracted, but when it attempted to hop, its head became wobbly and was thrown in all directions, and irregular contractions of the muscles of the extremities developed, causing the rabbit to fall to either side. The condition remained unchanged during the next two days, and the animal was found dead, March 24.

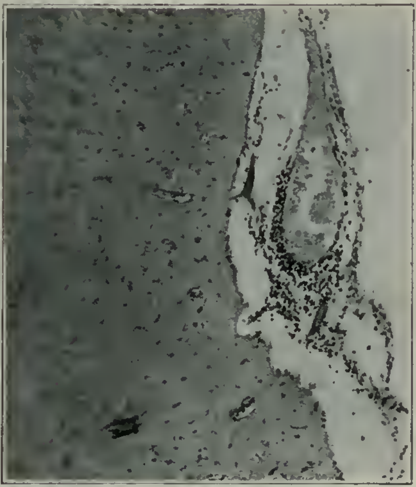

Figure 3

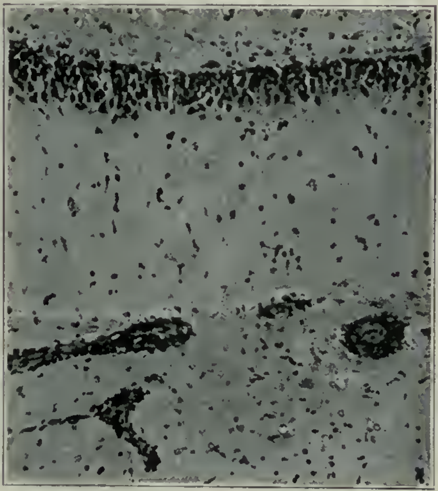

Figure 4

Fig. 3.—Lesions in the brain of Rabbit 2356 (see protocol).

Fig. 4.—Lesions in the brain of Rabbit 2356 (see protocol); hematoxylin and eosin; × 100.

No gross lesions were found. Cultures from the emulsion of the brain and the spinal fluid yielded countless numbers of the characteristic streptococcus; those from the blood, a few colonies.

Sections revealed marked leukocytic and round-cell infiltration in a sharply circumscribed area surrounding the point of inoculation; slight round-cell infiltration in the pia, most marked surrounding the vessels (Fig. 3), and several areas of marked perivascular infiltration in the subcortical region (Fig. 4) and in the cerebellum. Many diplococci were demonstrated in the area of marked infiltration at the point of injection, and a few in or adjacent to the other areas of infiltration (Fig. 5*a* and *b*). Two other rabbits injected with the same culture developed a similar train of remarkable symptoms.

Experiment 2.—Rabbit 3728, weighing 1,600 gm., was injected, June 30, 1922, with 0.2 c.c. of the salt solution suspension of the nasopharyngeal and tonsillar swabs from Case 4. July 1, at 7 a. m., the animal appeared excitable and hyperirritable, and had occasional twitching of the muscles of the fore extremities. At 9:30 p. m., it sat quietly humped up in the cage. When it was prodded, marked irregularly timed jerky movements of the head and extremities developed. July 2, it was excitable, turning its head from side to side, and often throwing it backward. Choreiform movements developed. During the following eight days, the condition remained much the same. July 11, it sat quietly in the cage most of the day, but on slight exertion it threw its head backward and from side to side. When prodded, its movements often became progressively worse, until it fell to either side, regaining its balance with some difficulty. There were no tremors nor spasms, and respiration was normal. The animal was chloroformed for examination. The vessels of the pia were congested; the cerebrospinal fluid was clear, but increased in amount, and the joints, muscles, myocardium and heart valves were normal.

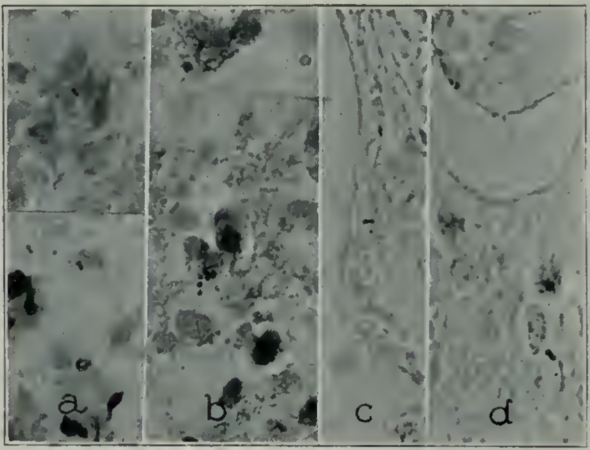

Fig. 5.—Diplococci in lesions of brain of rabbits: *a* and *b*, Rabbit 2356; *c*, Rabbit 3728; *d*, Rabbit 3764 (see protocols); gram stain; × 1,000.

Cultures from the blood were sterile; those from the brain yielded a few colonies of the characteristic streptococcus. Sections revealed perivascular infiltration in the subcortical region of the cerebrum; localized areas of slight infiltration in the pia, and an occasional diplococcus adjacent to dilated capillaries in the pia (Fig. 5*c*.)

Experiment 3.—Rabbit 3782, weighing 1,100 gm., was injected, July 18, 1922, with 0.1 c.c. of a 1 : 100 dilution in sodium chlorid solution of the culture from the brain of Rabbit 3728, in the fourth subculture. July 19, at 8 a. m., the animal appeared well. At 12 m., it had developed peculiar movements of the head, associated with vertical nystagmus, and irregular contractions of the muscles of the extremities which made it lose its balance at times. July 20, the choreiform movements of the head were less marked, but its head was slightly retracted and turned to the left. July 21, at 7 a. m., the animal was found dead.

Necropsy revealed extreme congestion of the vessels of the pia over the cerebrum; edema of the pia at the posterior junction of the medulla and cerebellum; marked cloudy swelling of the myocardium; large hemorrhages of the tricuspid valves, numerous large and small hemorrhages of the papillary muscles of the left ventricle, most marked at the apices; subendocardial hemorrhages in the septal wall of the left ventricle; nodular endocarditis of the mitral valve at the juncture of the chordea tendineae with the leaflet; several small subendothelial hemorrhages in the mitral valve (Fig. 6), and whitish lesions in the flat muscles of the lower abdomen and in the tendinous ends of muscles and ligaments around the left knee joint.

Cultures from the brain yielded a moderate number of colonies of the streptococcus; those from the blood, a few colonies. Cultures from the joint fluid, bile, liver and muscles remained sterile. Sections of the heart valves gram stained revealed a few diplococci in the hemorrhagic and nodular lesions of the mitral valve.

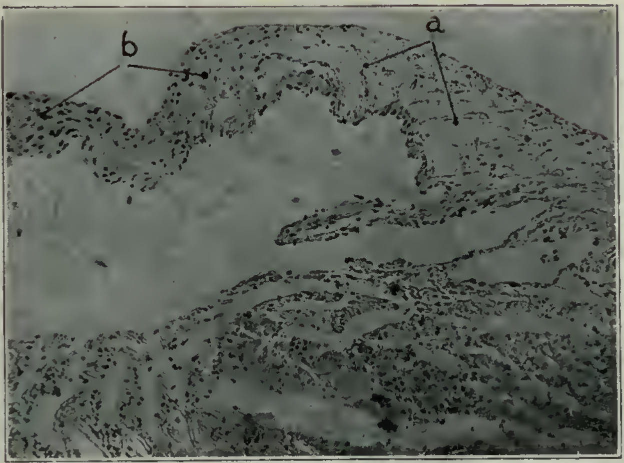

Fig. 6.—Subendocardial edema, *a*, and hemorrhage, *b*, in the mitral valve of Rabbit 3782; hematoxylin and eosin; × 100.

Experiment 4.—Rabbit 3764, weighing 1,810 gm., was injected, July 15, 1922, with 0.1 c.c. of a 1 : 10 dilution in sodium chlorid solution of the four-hour glucose-brain broth culture of the strain from the brain of Rabbit 3728 in the twelfth subculture. July 16, at 8 a. m., the animal was tremulous and ataxic; when standing, its whole body shook; and when it hopped, it tended to lose its balance, always falling to the left. At 12 m., the condition was much the same, but irregularly timed contractions of the muscles of the extremities, of varying intensity, had developed. At 6:30 p. m., the contractions of the muscles were worse, and, on exertion, choreiform movements of the head and the fore part of the body developed. July 17, there were extreme choreiform movements of the extremities. The animal became extremely ataxic and weak, and died.

Necropsy revealed marked congestion of the vessels of the meninges; localized hemorrhages of the pia over the lateral aspects of the cerebellum; edema of the pia over the posterior aspect of the cerebellum and medulla; hemorrhages of the tricuspid and mitral valves along the line of closure; one small hemorrhage at the base of the mitral valve, and an increase in the amount of cerebrospinal fluid, which was moderately turbid.

Cultures from the blood, kidney, liver and spleen were negative; whereas, cultures from the brain yielded a moderate number of colonies of the characteristic streptococcus.

Sections of the brain revealed moderate infiltration of the pia by leukocytes and round cells; slight perivascular infiltration in the subcortical region of the cerebrum, and marked invasion and infiltration of the cerebellar cortex by leukocytes (Figs. 7 and 8). Sections which were gram stained revealed a moderate number of diplococci in the areas of infiltration and in the adjacent tissues (Fig. 5*d*).

Experiment 5.—Rabbit 3755, weighing 1,900 gm., was injected intracerebrally, July 12, 1922, with 0.1 c.c. of a 1 : 1,000 dilution in sodium chlorid solution of the glucose-brain broth culture of the strain from Case 4, after two animal passages and in the second subculture. Blood-agar plate culture of the suspension injected yielded a pure growth of the green-producing streptococcus. July 13, at 12 m., the animal appeared well, but was somewhat wobbly, and when it hopped the fore part of the body tended to bob up and down. At 10 p. m., the fore part of the body bobbed more markedly, but more irregularly when the animal hopped, and peculiar choreiform movements of the head had developed. July 14, 15, 16 and 17, its condition remained about the same. In the interval from July 18 to July 27, the peculiar motions of the head and the bobbing of the fore part of the body became much less marked, and the animal appeared well when it was chloroformed, July 27. No gross lesions were found in the brain or the cord.

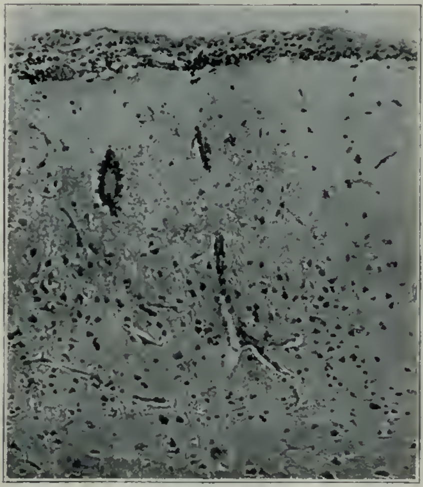

Figure 7

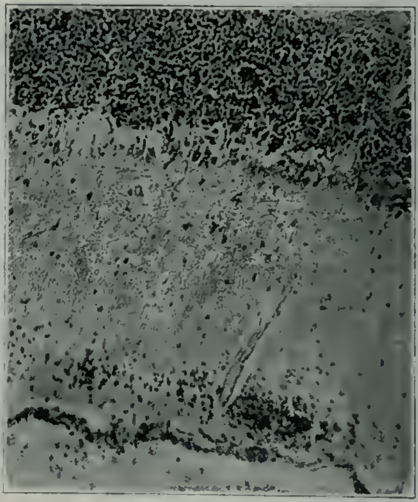

Figure 8

Fig. 7.—Moderate infiltration of pia over cerebral cortex; slight perivascular, and no parenchymatous infiltration (Rabbit 3764); hematoxylin and eosin; × 100.

Fig. 8.—Marked parenchymatous infiltration of cerebellum of Rabbit 3764; hematoxylin and eosin; × 100.

Cultures from the blood and the brain remained sterile. Cross-sections of the middle portion of the cerebellum revealed moderate localized perivascular round-cell infiltration of the pia (Fig. 9), and occasionally around the blood vessels within the substance of the cerebellum. In some instances, the infiltration was limited to that part of the vessels adjacent to the brain. Cross-sections of the posterior part of the right cerebellar hemisphere revealed a localized area of infiltration near the third ventricle, and a longitudinal section of the left cerebral hemisphere near the median line revealed an area of considerable size in which there was diffuse parenchymatous and perivascular round-cell infiltration (Fig. 10). In one vessel in this area, the lumen was almost occluded by infiltration with round cells within the wall of the vessel. No infiltration was found in the pia over the cerebellar cortex. There was no lesion at the point of inoculation, and none in the medulla.

The gross and microscopic findings in the central nervous system following intracerebral inoculation varied greatly, depending on the virulence of the strain, the amount of the culture injected and the resistance of the animals. In the animals that died soon after inoculation, moderately turbid cerebrospinal fluid and congestion of the vessels of the meninges were usually found, and occasionally localized hemorrhages in the pia. Aside from an occasional area of infiltration at the point of inoculation, gross lesions in the brain or cord substance and suppurative meningitis were not found. Sections showed a widespread but usually relatively slight leukocytic infiltration of the pia, most marked over the cerebral cortex; and at times, leukocytic and round-cell infiltration of the choroid plexus. In the animals that died late or were chloroformed for examination, evidences of diffuse meningitis were usually absent, and, as a rule, no gross lesions were found. Microscopic examination often revealed localized and perivascular infiltration in the pia (Figs. 3 and 9), and localized (Fig. 10) and perivascular infiltration, chiefly by mononuclear cells, in the subcortical region, in the pons, in the cerebellum and not infrequently in the choroid plexus. The degree of involvement was often directly proportional to the severity of symptoms, and the location of the most pronounced microscopic changes corresponded to that indicated by particular symptoms noted during life.

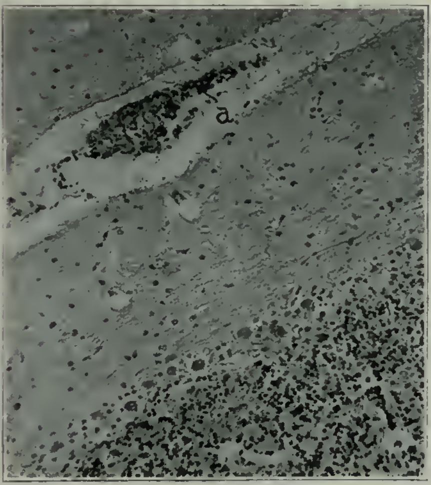

Figure 9

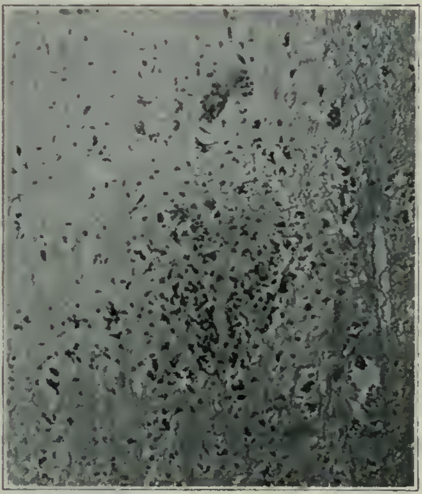

Figure 10

Fig. 9.—Localized perivascular infiltration of pia at *a*, in cerebellum of Rabbit 3755; hematoxylin and eosin; × 100.

Fig. 10.—Parenchymatous infiltration in the cerebrum of Rabbit 3755. This lesion is similar to those shown in Figures 2 and 13; hematoxylin and eosin; × 100.

RESULTS FOLLOWING INFECTION OF TEETH IN DOGS

Since the tendency of this strain to localize in a characteristic manner was so marked on both intravenous and intracerebral inoculation, it was thought worth while to determine whether localization would also occur through foci of infection, thus simulating the condition in the patient from whom this strain was isolated, and in whose tonsils foci of infection were found. Accordingly, the cuspids in each of four healthy, active dogs were sterilized. A rubber dam was applied; and, after the ends of the teeth were cut off, they were reamed with dental burrs; the pulps were extracted under intratracheal ether anesthesia; a dense suspension of a mixture of the actively growing streptococcus in the first, second, and third animal passages was inoculated into the canals, and the openings were sealed with dental cement. A part of the suspension of the streptococcus used to infect the teeth of these dogs was injected intravenously into two dogs. Six days after injection, one of the dogs developed rhythmic contractions of the muscles of the left shoulder and the left leg, which lasted for about a week. The animal was chloroformed seventeen days after injection.

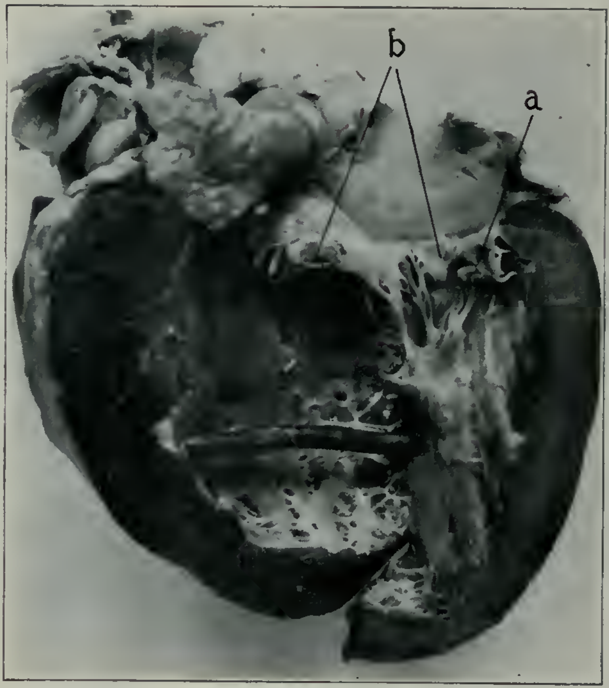

Fig. 11.—Nodule, *a*, and vegetations, *b*, endocarditis of mitral valve in a dog injected intravenously with the streptococcus from Case 4.

Necropsy revealed a chocolate-colored edematous infiltration along the base of the mitral valve. The other dog appeared sick on the third day after injection. For several days, it protected the right foreleg, as if it were painful. It seemed prostrated, and when made to walk became short of breath. No symptoms resembling chorea developed. The animal was chloroformed eighteen days after injection. Necropsy revealed a firm, elongated, hemorrhagic vegetation (3 by 5 by 7 mm.) of the posterior leaflet of the mitral valve, originating along the line of closure (Fig. 11); an area of thickening with ulceration along the line of closure of the anterior leaflet, directly opposite another vegetation on the posterior leaflet (Fig. 11), and several subendothelial nodules nearer the base of the posterior leaflet of the tricuspid valve.

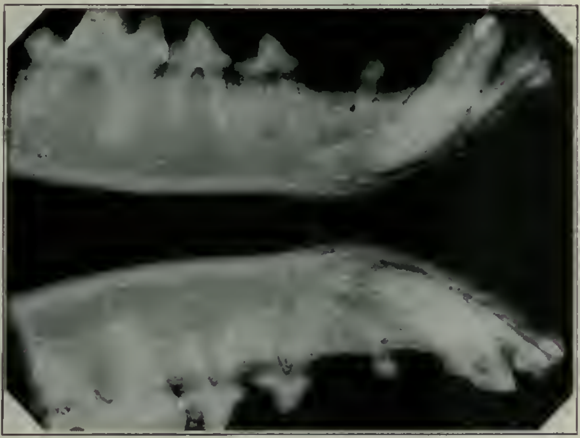

Fig. 12.—Areas of rarefaction at the apices of the roots of the lower cuspids of the dog that developed chorea following devitalization and infection of the teeth with the streptococcus from Case 4.

The strain inoculated into the devitalized teeth had retained specific infecting power over a period of three months.

Sections through the vegetations on the mitral valve revealed moderate leukocytic infiltration in and around the base of the fibrin deposit, in which a few cells, chiefly leukocytes, were found. No microscopic lesions were found in the myocardium.

Two of the dogs whose teeth were devitalized and infected remained well, while two developed muscular movements resembling chorea. In one, marked shivering spells and rapid twitchings of the muscles of the fore and hind legs developed the following day. This continued for about three weeks, when complete recovery ensued.

The findings in the other dog were as follows: The day after inoculation (July 25, 1922), the animal appeared nervous, and there was repeated contraction of the left foreleg and the muscles of the fore part of the body, which it tried to control by crouching to the floor of the cage. The following day, it blinked frequently; the condition in the left foreleg had become more marked, and the animal still tried to control the muscular contractions, by lifting the leg from the floor and by crouching to the floor. This condition remained unchanged for three weeks, following which the muscular contractions gradually grew less marked; but they were still present, September 4, when the animal was chloroformed. There was no loss in weight. The devitalized and infected teeth were discolored, but firmly in place. There was no swelling opposite the roots. Roentgenograms of the lower jaw revealed decided areas of rarefaction around the root apices (Fig. 12).

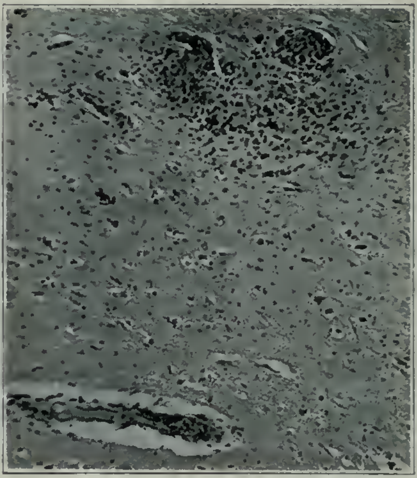

Fig. 13.—Area of parenchymatous and perivascular infiltration in the subcortical area of the middle rolandic region of dog referred to in Figure 12; hematoxylin and eosin; × 100.

The pulp chambers were filled with thick chocolate-colored pus, in which large numbers of diplococci and streptococci were found, and from which the inoculated streptococcus was isolated in large numbers, together with a few gram-negative bacilli. The vessels of the meninges appeared congested. The cerebrospinal fluid was clear, but increased in amount. There were no gross lesions of the brain, but a small area of hemorrhagic infiltration was found in the posterior leaflet of the mitral valve.

The blood and brain yielded pure cultures of the streptococcus resembling the one isolated from the infected teeth. Microscopic examination of sections of the brain revealed areas of slight localized and perivascular infiltration in the pia over the cerebrum and cerebellum; small hemorrhages in the subcortical region, often surrounding small vessels, associated with leukocytic infiltration; several areas of parenchymatous and perivascular round-cell infiltration in the subcortical region of the cerebrum (Fig. 13) and in the pons, most marked near the median line just anterior to the cerebellum (Fig. 14), and moderate neurophagocytosis surrounding the areas of perivascular infiltration. By far the largest portion of the sections examined were free from lesions. Painstaking search for bacteria revealed a few gram-positive diplococci in, and adjacent to, the fresh perivascular hemorrhages, with slight leukocytic infiltration. No bacteria were demonstrable in the areas of pronounced round-cell infiltration, nor in the normal tissues.

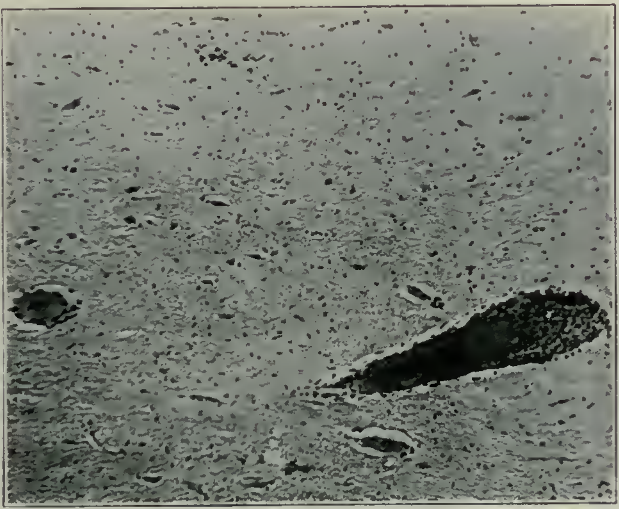

Fig.14.—Area in pons in region of cerebellar peduncles showing perivascular round-cell infiltration in dog referred to in Figure 12; hematoxylin and eosin; × 100.

The strain isolated from the brain of this dog was injected intravenously into three rabbits, 1 c.c., 3 c.c., and 5 c.c., respectively, of the glucose-brain broth culture, in the second generation. The strain from the blood was injected intravenously into two dogs, after 2 c.c. of normal horse serum had been injected intracerebrally to facilitate localization. The rabbits remained free from symptoms and were chloroformed for examination three days after injection. The one receiving 5 c.c. showed no lesions. The one receiving 3 c.c. had hemorrhagic lesions on the inner and anterior aspect of each tibia, and the one receiving 1 c.c. had small hemorrhages in the posterior leaflet of the mitral valve. One of the dogs developed twitchings and irregular contractions of the muscles of the neck and of the left leg, two days after injection. This lasted for several days, then disappeared, and the dog remained apparently well. When it was chloroformed fifty-two days later, no lesions were found. The other dog remained free from symptoms, and was chloroformed one week after injection. Necropsy revealed edema; nodular thickening along the line of closure of the mitral valve, and hemorrhages between the cusps of the aortic valves and in the papillary muscles. The tricuspid and semilunar valves were free from lesions.

The streptococcus inoculated into the pulp canals was isolated from one or more teeth in each dog when they were chloroformed, three months later. Roentgenograms of the lower jaw in the two dogs that remained well were negative; whereas, in the two that developed chorea-like symptoms, small areas of rarefaction filled with granulation tissue had developed (Fig. 12). The blood and brain were found sterile in the three that were free from symptoms when chloroformed.

SUMMARY AND CONCLUSIONS

Characteristic localization followed intravenous and intracerebral inoculation as well as the infection of teeth in dogs. The lesions were due to the same streptococcus, regardless of the fact that mixtures of bacteria in the suspensions and primary cultures were sometimes injected. The property on which specific localization depended was retained through three successive animal passages, after many rapidly made transfers of pure cultures, and for as long as three months in the teeth and brain of the dog. The specificity as regards both the infecting power and the immunologic properties was lost after ordinary aerobic cultivation. The symptoms produced were strikingly like those in chorea in man. The experimental lesions in the central nervous system, aside from a low grade meningitis, resembled in type and location the lesions in human beings as described by various observers, and were found chiefly within or adjacent to motor centers or motor paths in the cerebrum, in the midbrain and in the cerebellum. The extent and location of the lesions often corresponded to the severity and type of symptoms observed during life. Moreover, the lesions in the heart valves resembled those noted in chorea in man, in location, in gross appearance and in microscopic findings. The organism was demonstrated in, or adjacent to, the lesions, and proved absent in normal tissues on microscopic examination. The symptoms paralleled those noted clinically in type and degree; and, in the experiment on the teeth in dogs, in which the condition in patients was most closely simulated, in duration as well.

Many similar experiments which serve as controls were performed with strains isolated from cases of encephalitis, epidemic hiccup and ulcer of the stomach (as summarized in the accompanying table), and also from the throats of normal persons, and persons suffering from poliomyelitis. In these experiments, localization rarely occurred in heart valves, joints or muscles; and except in myoclonic types of encephalitis, the lesions in the central nervous system did not induce symptoms like those following injection of strains from chorea.

In view of these results and the findings reported by others, the conclusion that chorea is due to a streptococcus having peculiar neurotropic, immunologic and other properties seems warranted.

BIRTH HEMORRHAGE INTO THE SPINAL CORD WITH RESULTANT BLADDER AND KIDNEY COMPLICATIONS *

REPCRT OF A CASE

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DULUTH, MINN.

Cases of birth hemorrhage into the spinal cord, though they probably occur more frequently than is generally supposed, are not numerous in the literature. Most work on the subject has been done quite recently.

The most comprehensive article on this condition is that of Crothers,[1] who quotes Head and Riddoch[2] at some length. These investigators studied the effect of cord injuries in young men wounded during the World War, and they conclude that high physiologic transections of the cord in healthy young men run the following course:

First stage: There is muscular flaccidity, with a lack of tone in the skeletal muscles, anesthesia, dryness of the skin, which is easily marred, and retention of urine and feces.

Second stage: After a few weeks, reflexes appear. At first, stimulation of the sole causes various toe movements; later, a variety of flexion responses of the legs and lower abdomen can be elicited. With severe stimulation, both legs and recti abdominis share in a vigorous "mass" reflex which is accompanied by evacuation of the bladder. The easy elicitation of this "mass" reflex, accompanied by sweating, is characteristic of this stage of reflex activity. Tendon jerks and other signs of extensor excitability are later signs. The bladder action becomes "automatic," the organ emptying itself at definite degrees of pressure without other stimulation, or at lower pressures when the mass reflex is elicited.

Third stage: As sepsis of serious importance intervenes, the reflex activity subsides, and sometimes never returns. Obviously, sepsis occurring prior to the second stage may prevent the occurrence of reflex activity of any kind.

Crothers quotes several authors, notably Ruge, Warwick and Stoltzenburg, to show that babies dying of asphyxia shortly after breech delivery give evidence of cord injury in a considerable per-

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* Received for publication, July 9, 1923.

* From the department of Pediatrics of the Duluth Clinic.

[1] Crothers, Bronson: Injury of the Spinal Cord in Breech Extraction as an Important Cause of Fetal Death and of Paraplegia in Childhood, Am. J. M. Sc. **165**:94-110 (Jan.) 1923.

[2] Head, H., and Riddoch, G.: Brain **40**:188, 1917.

centage. He deems it likely, in the light of the work of Head and Riddoch, that, if such babies survive, they will show a high degree of reflex excitability, provided the lesion is not high enough to involve the medulla or phrenic nerves or low enough to destroy the lumbar enlargement. Under favorable circumstances, indefinite existence seems quite possible. Crothers cites five cases of his own, in which the ages ranged from 2 weeks to 12 weeks. All of these cases gave a history of breech delivery. He draws the following conclusions:

1. High cervical transections of the cord are probably all fatal on account of the proximity of the lesion to the phrenic nerves and the medulla.

2. Transection below this fatal level, if accompanied by enough hemorrhage to destroy the cells of the lower segments, results in anesthesia and permanent flaccidity.

3. Transection confined to a few segments and not involving the lumbar enlargement will show, in succession, the following symptoms: (*a*) Anesthesia with flaccid paralysis. After a few days or weeks, the flaccid paralysis will be modified and the infant will show (*b*) anesthesia as before, a zone of flaccidity corresponding to the destroyed anterior horn cells, and below this zone reflex activity of distinctive type. During this stage, the action of bladder and rectum becomes automatic. On theoretical grounds, it seems likely that this stage of reflex activity will last only so long as severe infection is avoided.

4. It is evident that the vast majority of obstetric spinal cord injuries are incident to maneuvers in breech extractions. He considers the high percentage of this condition following breech extraction due to the following factors peculiar to this type of presentation: (*a*) Traction exerted over the entire length of the spinal column. (*b*) Pressure on the head, resulting from intra-uterine contraction or due to suprapubic pressure by the operator or assistant. The spinal cord of the baby is firmly anchored below by the cauda equina and above by short, heavy, almost horizontal, spinal roots. Its upper end is continuous with the medulla. When the spinal column becomes elongated through traction, one or two possible accidents may occur. The cord may give, with resultant hemorrhage and even rupture, or it may hold and pull down the structures above so that fatal herniation of the medulla into the foramen magnum may result. Death in this case, Crothers considers due to increased medullary pressure, resulting in vasomotor collapse; or to extreme vagus stimulation.

The work of Crothers is of great importance and, though based on theory to a great extent, as he admits, gives us a new point of view and should stimulate further investigation.

Kooy[3] reports the case of a child born by version, in which there was nearly complete rupture of the cord at the level of the ninth and tenth thoracic segment. The child lived for nine years, with almost complete anesthesia; incontinence of urine and feces, and spasticity of the legs. Microscopic examination of the cord postmortem revealed practically complete destruction at the above mentioned level, the only long tract left intact being the ventral pyramidal tract.

Burr[4] reports two cases of hemorrhage into the spinal cord at birth following breech delivery. The first was seen at the age of 4½ months. Necropsy demonstrated practically complete destruction of the lower cervical cord. The child's head was pulled back; there was the characteristically flexed position of the upper arm and forearm; the breathing was entirely diaphragmatic, and there was palsy of the thoracic and abdominal muscles and flaccid palsy of both legs. In the second case, the child was seen at the age of 3 months. The findings were quite similar to those in the first case. The child died and there was no necropsy. Both of these births were breech deliveries.

Burr quotes Spencer, who performed a series of necropsies on 130 fetuses, the majority still born, in which the spinal cord was examined in forty-four cases. In thirty of these forty-four cases, there was hemorrhage somewhere within the spinal canal; and, of these thirty cases, it was within the spinal cord in six. From his statistics, Spencer concludes that spinal hemorrhage is greatly favored by presentation of the lower extremity. He thinks the increased liability to hemorrhage is due partly to the great pressure on the soft parts, with resultant driving of the blood to the central organs, and partly to the fact that traction is sometimes employed. Spencer regards the normal delicacy of the fetal blood vessels as the one essential feature in the causation of hemorrhage.

Burr considers the cause of the hemorrhage in his case, which came to necropsy as most likely due to rupture of overfull vessels from pressure on the soft parts during birth.

Leavitt[5] reports a case of spinal cord hemorrhage in a child born by breech extraction, with flaccid paralysis below the site of hemorrhage; characteristic position of the arms, and flaccid paralysis of the chest and abdominal muscles, and sphincters of bowel and bladder.

I observed the subjoined case of hemorrhage into the cervical cord, at birth and at frequent intervals thereafter until the child died, at the age of 9 months.

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[3] Kooy, F. H.: J. Nerv. & Ment. Dis. **52**:1 (July) 1920.

[4] Burr, C. W.: Hemorrhage into the Spinal Cord at Birth, Am. J. Dis. Child. **19**:473-477 (June) 1920.

[5] Leavitt, F. H.: Arch. Pediat. **39**:758, 1922.

REPORT OF CASE

History.—G. K., was born, Feb. 19, 1922, of Greek parentage. The mother and father, were living and well. There had been no previous pregnancies, and there was no history of any chronic disease. The birth was a breech delivery, both feet presenting. Delivery was not unusually long, although the head was rather difficult to disengage.

Examination.—The child was seen by me the day after birth, when I made the following notes: "Weak cry, listless, cold, breathing practically all diaphragmatic."

For the next ten days, it was seen daily, the case running the following course: The child remained weak; the cry was poor, and the breathing was entirely diaphragmatic. The chest was pulled in and the abdomen ballooned. Pressure on the abdomen frequently resulted in urination. There was some movement of the arms and legs. Sensation was not tested. Tension at the fontanel was normal. On the fourth day, coagulation time was twelve minutes (Rodda method); bleeding time, four minutes (Duke method). Spinal puncture performed on this day revealed a xanthrochromic fluid, there being numerous blood cells microscopically.

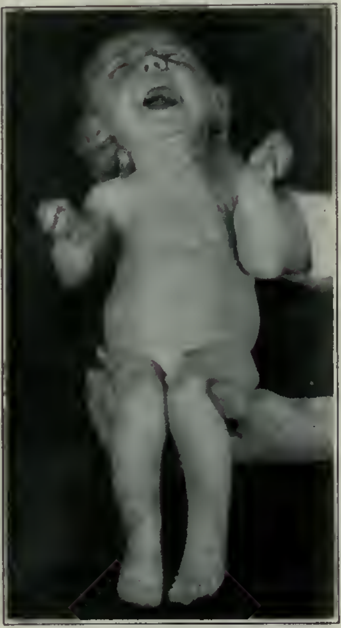

Fig. 1.—Patient at 3 months of age. The position of arms and hands, retraction of head and pulling in of chest are evident.

Treatment and Course.—The child was given three intramuscular injections of the father's blood, of from 15 to 30 cm. each, during the next few days. Spinal puncture on the sixth day again gave a xanthrochromic fluid. There was no evidence of bleeding elsewhere. While in the hospital, the baby became markedly icteric. On the ninth day, it was noticed that it held the arms close to the body, flexed at the elbow, and moved the forearms and hands fairly well. The icterus became less; the general condition improved, and the child was discharged from the hospital at the age of 2 weeks.

From this time on, it was seen at frequent intervals.

At 1 month, the paralysis of the intercostals was marked; the abdomen large, and the respiration was entirely diaphragmatic. The arms were held in a rather fixed position of flexion at the elbow, and dorsiflexion of the hands, The impression of hemorrhage into the cervical cord at birth was retained. Attempts to elicit changes in sensation were unsatisfactory.

The Wassermann reaction of the mother and of the child at 6 weeks of age were negative. A note at the age of 7 weeks says: "Legs limp, poor strength, knee jerks present."

At 2 months, the child became ill with fever. It was listless, and there was a tendency to hold the head back. Nystagmus was noted, with the quick component to the left. The pulling back of the neck was first noticed here, though probably present before, the head being set down on the shoulders. This condition continued through life. A roentgenogram of the cervical spine at this date revealed no definite abnormality. The child was sent to the hospital, where it remained for two weeks, running an irregular septic temperature due to a rhinopharyngitis and otitis media. Several urine examinations during this period revealed a few pus cells, insufficient, however, for a diagnosis of pyelitis. The child gradually recovered, and was sent home, where it did well for three or four weeks.

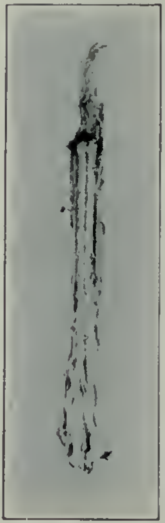

Fig. 2.—Spinal cord as removed at necropsy. There is degeneration in the cervical region, with adhesions to the dura.

At 3½ months, the child became febrile again, without ascertainable cause. The pupils were markedly contracted, and remained so thereafter. They responded slightly to light. For the next month and a half, there was intermittent fever. Finally, at 5 months, the urine was found to be full of pus, which was so thick that it was plainly visible in the bottom of the centrifuge tube. The bladder could be palpated almost up to the umbilicus through the thin, weak abdominal wall. Pressure on the abdomen invariably caused urination. At this time, elicitation of the knee jerks on one side frequently caused clonus of the opposite leg to appear. Vigorous treatment for the pyuria was at once instituted and was continued over a long period. Large amounts of water were given, and sodium bicarbonate and hexamethylenamin alternated. Several injections of horse serum were given intramuscularly. Culture of the urine yielded colon bacilli. An autogenous vaccine was made and given over a period of several months. None of these methods were of any avail. The urine remained full of pus and continued so for four months, until the time of death. For most of this period, the child ran a septic temperature, frequently up to 103 or 104 F. The kidneys increased in size and could be easily palpated in either loin. It is remarkable that the child gained weight in spite of the severity of the infection.

At 8½ months, a severe rhinitis became manifest. This soon developed into the bronchopneumonia which caused death, at the age of 9 months.

Necropsy Findings.—The general appearance was as during life: the abdomen large; the chest pulled in; upper arms close to the body; forearms flexed at the elbow; hands dorsiflexed at the wrist.

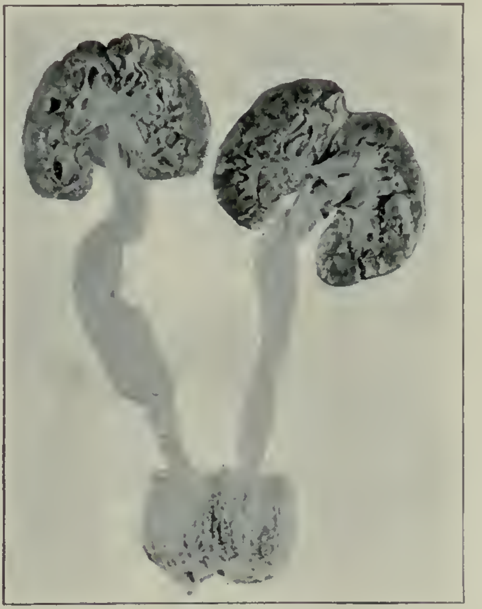

Fig. 3.—Section of urinary system. There is dilatation of the ureters and pelves, and hemorrhagic inflammation of the bladder wall.

Thorax: The heart showed no anomalies. The thymus was normal in size and appearance. In the lungs, there were numerous areas of consolidation in all lobes.

Abdomen: The gross appearance of all organs except the urinary tract was normal. The kidneys appeared larger than normal. They were mottled grayish red, and the surface showed fetal lobulations. The ureters on either side are equally enlarged, the diameters being about 1 cm. The increase in diameter was uniform from the pelvis to the bladder wall. Section of the kidneys revealed that the pelves were dilated; the surface of the pelves had a rather thickened, granular appearance. The walls of the ureters appeared thickened and ragged. The parenchyma of the kidneys was softer than normal. Section of the bladder showed that the wall was thickened, and the surface was thrown into numerous rugae, which were red and inflamed. The ureteral openings appeared normal. A tiny probe could be passed into each ureter without difficulty. There was no apparent obstruction at the bladder wall or above. The bladder, ureters, and pelves contained a large amount of free pus diluted with urine.

Permission being granted only to remove the cord, as much as could be reached from below was dissected away. Gross examination of the cord revealed that the cervical region, as high up as it was removed, consisted of only a small column of tissue, scarcely half the size of that portion of the cord below. This apparently contained little or no nervous tissue, and appeared to be fibrous. It adhered tenaciously to the dura mater. Below this level, the cord appeared practically normal.

Sections of the organs were sent for microscopic study to Dr. E. T. Bell of the pathologic department, Minnesota University Medical School, who reported: "Section of the cord at the site of the lesion shows complete degeneration of all tracts. Below this level there is marked degeneration of the pyramidal tracts, especially in the crossed pyramidals. The kidney shows hydronephrosis, with chronic pyelonephritis. The ureters are dilated, and show practically no disease. There is a low grade, chronic inflammation of the mucous membrane of the bladder. The condition of the urinary tract is evidently due to the spinal cord lesion, with subsequent infection."

At Dr. Bell's suggestion, a section of the cord was sent to Dr. Ernest Sachs, neurologic surgeon to the Washington University Medical School, who reported: "The section shows degeneration of the direct and crossed pyramidal tracts. The lateral portion of the cord is not myelinated, and both the dorsal and ventral cerebellar tracts are involved, the dorsal less so than the ventral. The order of myelinization of these tracts is: ventral, dorsal, pyramidal, and in a child of 9 months, the dorsal tract should be myelinated, which it is not in this section. This may be explained by the hemorrhage at a higher level."

SUMMARY

1. In a case of hemorrhage into the cervical cord at birth, the child was born by breech extraction, some difficulty being encountered with the aftercoming head. The hemorrhage I consider due to trauma incident to delivery rather than to abnormal condition of the blood, in spite of a slight prolongation of the coagulation time. There were no evidences of hemorrhage elsewhere, as is the frequent finding in hemorrhagic disease of the new born. Spinal puncture on the fourth day of life revealed only old blood. The hemorrhage was evidently below the level of origin of the phrenic nerves as the diaphragm functioned normally. Necropsy revealed a complete degeneration of the cord in the lower cervical region and degeneration of various tracts at lower levels.

2. The child showed the typical picture of cervical cord injury. The position of the arms was characteristic. The breathing was entirely diaphragmatic, there being paralysis of the thoracic and abdominal muscles. The legs were paralysed.

3. As a result of bladder paralysis with back pressure, the child developed double hydro-ureters and hydronephrosis. Infection resulted in both bladder and kidneys. As would be expected, this infection did not respond to any treatment.

4. Movements of the legs were noticed a few days after birth. Knee jerks were elicited at 7 weeks, the response being weak, however. At the age of five months, attempts to elicit knee jerks on one side resulted in clonus of the entire opposite leg. No satisfactory sensory tests were obtained.

A FATAL CASE OF THRUSH INVOLVING THE SKIN, LUNGS AND NAILS *

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ST. PAUL

Thrush, as a generalized disease, is a rare condition, presenting not only points of unusual interest but also a baffling problem in treatment. Therefore, when one such case was seen and studied for a period of three years, it was considered of enough importance to be reported. A comprehensive search of the literature yielded only two references.[1]

REPORT OF CASE

D. W., a girl, born Jan. 16, 1917, weighing, at birth, 7 pounds (3,175 gm.), the youngest of a family of four girls, at the age of 5 months suffered an attack of bronchopneumonia complicated with cervical adenitis and otitis media. (The discharge from the ears persisted up to the time of death.) In March, 1919, the patient had an attack of influenza, which lasted a few days. In April of the same year, the mother noticed an inordinate amount of "drooling," with coated tongue and grayish white patches covering the mucous membrane of the mouth. A diagnosis of thrush was made at this time, and ordinary remedies were used without any appreciable change in the condition during the next six months. In the late summer, the child began to have frequent attacks of vomiting, accompanied by a very fetid odor of the breath.

From October, 1919, to February, 1920, she was kept on a diet consisting almost exclusively of vegetables and fruits. In November, 1919, it was noted that the index finger of the left hand had become infected. Shortly afterward, a brownish red spot, with a clearly defined outline, and covered with fine, branny scales, developed on the back of the neck. This at first was thought to be in the nature of ringworm, but scrapings from this area showed the characteristic *Oïdium albicans.* This rapidly spread until the entire scalp became involved, the eruption having much the appearance of a dry seborrhea.

Since none of the remedies previously used seemed to have any appreciable effect on the progress of the disease, the child was sent to Dr. W. P. Larson, professor of bacteriology at the University of Minnesota Medical School, with a request that he make a complete examination of the various lesions and endeavor to procure a vaccine. Scrapings taken from the mouth, skin and finger nails all showed *Oïdium albicans.* Washed sputum showed the same organism. The sputum was repeatedly subjected to a searching and exhaustive examination, the results always being the same. From these cultures, a vaccine was made. The patient received in all sixteen injections. A marked improvement in the clearing up of the mucous membrane of the mouth was apparent after the second injection, but the effect was not of long duration.

It was noted at about this time that the skin of the face was becoming involved. This condition gradually spread until, at the time of death, nearly the whole of the face was covered with the eruption; this, with eruptions on the entire scalp, the left hand, the nails of that hand, the back of the right

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* Received for publication, July 19, 1923.

* From the Miller Hospital Clinic and the Pediatric Department of the University of Minnesota Medical School.

[1] Schamberg: Arch. Pediat., August, 1915, p. 617. Sasamoto: Jap. Ztschr. f. Derm. & Urol. **20.**

hand and wrist, and several areas on the chest and about the vulva, together with the chest findings, the cough and expectoration and the severe vomiting made a most distressing picture.

Various changes were made from time to time in the child's diet, but as none of these seemed to influence the condition in any way, she was allowed anything she wished. The eruption gradually extended over the entire left hand, the finger nails assuming a thickened, clawlike appearance. At times, the nails dropped off, only to be replaced by others of increased thickness.

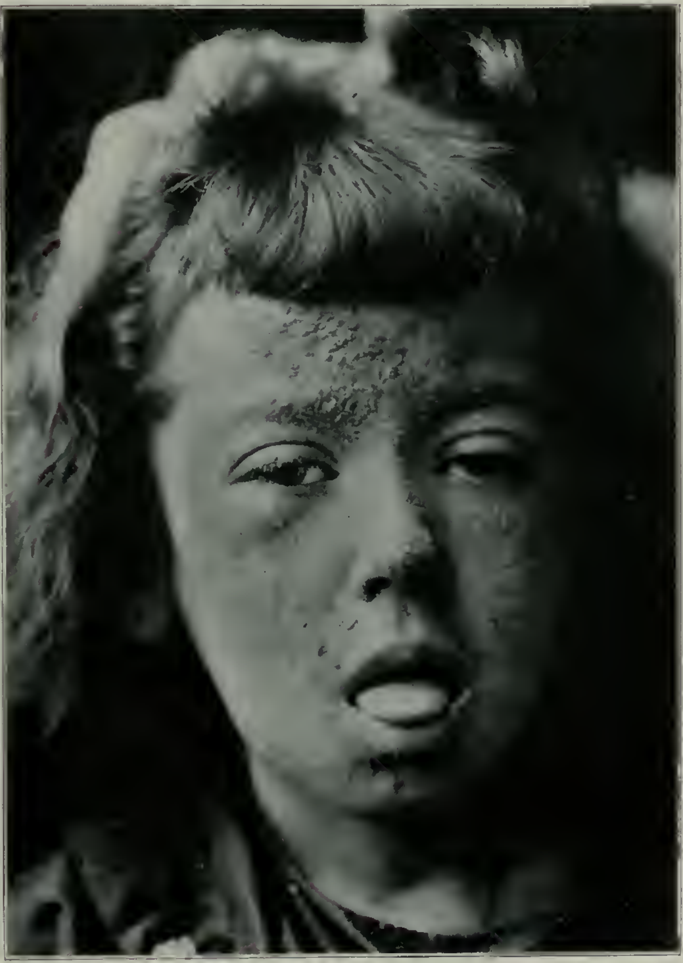

Fig. 1.—Appearance of child shortly before death.

During the summer and autumn of 1920, the condition progressed slowly. Vomiting became less frequent, though a more or less persistent cough had developed. Examination of the chest led to the belief that the thrush was gradually involving more of the lung tissue. For the next succeeding six months, little change was noted.

In June, 1921, the patient was taken to North Dakota for a visit. While there, she seemed to improve in general health, but the condition of the mouth and skin remained unchanged. About this time, the thrush appeared on the right wrist, spreading slowly upward and downward. The child, when seen on her return to St. Paul, September 1, weighed 28 pounds (12.8 kg)—her greatest weight. The skin condition had not improved.

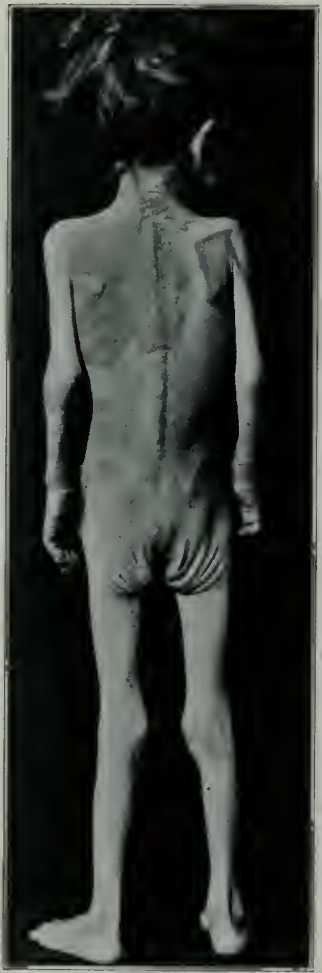

Fig. 2.—Appearance of patient shortly before death.

October 10, she was taken suddenly ill with what was at first thought to be pneumonia, but what was probably an acute exacerbation following a fresh invasion of lung tissue by the advancing thrush. Recovery was slow, the cough persisting and at times causing much distress. A similar attack occurred about July 1, 1922. On two or three occasions, small quantities of bright red blood appeared after one of the more severe paroxysms of coughing. From this time on, the child grew gradually weaker, until death occurred, September 2, from exhaustion. Necropsy was not obtained.

COMMENT

The outstanding features of this case, aside from the severity of the skin eruption, were the very offensive odor of the breath in the early stages, suggestive of gangrene of the lung; the continuous vomiting and the harrassing cough, and the progressive emaciation and pronounced muscular weakness.

The treatment consisted in a trial of all the well-known remedies usually applied in thrush and, in addition, arsphenamin, iodids, the roentgen ray, mercurial inunctions and a vaccine prepared from scrapings taken from the various lesions. During the period of illness (two and one-half years), the child was seen by several of our confreres, and in every instance the laboratory findings confirmed the diagnosis. Wassermann, blood and urinary findings were always negative.

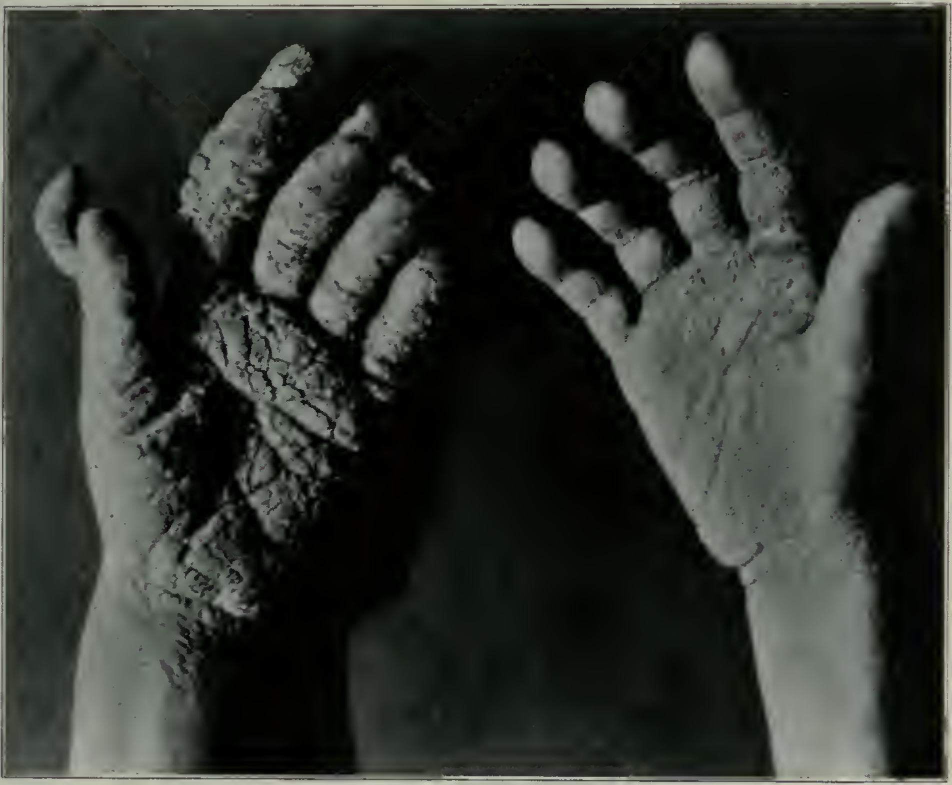

Fig. 3.—Appearance of hands of patient shortly before death.

Figures 1, 2 and 3 show the condition as it existed shortly before the child's death.

PHYSIOLOGY OF EXERCISE IN CHILDREN.

PART 2. STUDY OF COLLAPSE IN NORMAL CHILDREN *

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AND
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In Part I of this study,[1] we presented the results of our investigation of the maximum physical capacity of normal schoolchildren and of the effect of maximum physical effort on the circulatory reactions.

It is the consensus of opinion among investigators that, in normal persons, after moderate amounts of exercise, there is always an increase in the pulse rate and in the systolic blood pressure. However, the opinions vary regarding the effect of exhaustive exercise on the circulatory reactions, especially in the event of collapse. A review of the extensive literature on this subject leaves one confused and in doubt. The reasons for this are: 1. No one has ever established a normal quantitative standard of physical capacity for work. This applies to adults as well as to children. 2. The technic employed lacks uniformity. 3. No careful and comprehensive attempts have been made, either by the physiologist or by the clinician, to compare the experimental data obtained in normal conditions with those obtained in diseased conditions.

In this paper, we attempt to answer the following questions.

1. What are the circulatory reactions in normal children who have surpassed the limit of their physical capacity?

2. What is the physiologic explanation of the curves described below?

3. What is the clinical significance of these curves?

Katzenstein,[2] in 1903, was among the first to study the systolic blood pressure and the pulse rate in fatigue resulting from prolonged muscular effort. He does not publish any curves, but he states as the general conclusion that the pulse rate and the blood pressure register a drop after cessation of exhaustive exercise. Heichelheim and Metzger,[3] in 1906, studied the circulatory reactions in twelve young

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* Received for publication, June 29, 1923.

* From the Department of Pediatrics, University of Minnesota Medical School.

[1] Seham, Max, and Egerer-Seham, Grete: Physiology of Exercise in Childhood, Part 1, A Study of Normal Children of School Age, Am. J. Dis. Child. **25**:1 (Jan.) 1923.

[2] Katzenstein: Ueber eine neue Funktionsprufung des Herzens, Deutsch. med. Wchnschr. **30**:807-809, 1904.

[3] Baldes, Heichelheim and Metzger: Untersuchungen über den Einfluss grosser Körperanstrengungen auf den Zirkullationsapparat der Nieren und des Nervensystem, München. med. Wchnschr. **53**:1865-1866, 1906.

athletes, from 17 to 27 years of age, at the end of a 100 kilometer run at top speed. They claim to have found that the blood pressure was lowered 25 per cent. They omit the time of their readings; nor do they mention for how long a period after exercise they continued their determinations. Potter and Harrington,[4] in 1909, studied the effect of Marathon runs (from 10 to 20 miles) on young athletes. They, too, noticed a lowering of the blood pressure after the runs. Barach, in 1910, took blood pressure readings of athletes, 19 years of age, after Marathon runs. The average systolic blood pressure before the race was 126.5 mm., as against 107.5 mm. after the race. In every instance, there was a fall of the blood pressure below normal.[5] Lowsley, in 1911, investigated the effect on athletes of all types of athletics, from mild games to the most exacting Marathon runs. His work is most accurate and comprehensive. He observed that, after violent running, the blood pressure as well as the pulse rate drops precipitately, remaining below the preexercise level for long periods. In fatiguing, 6-mile runs, the subnormal phase persisted for from four to five hours. In 20-mile races, the men were carried off in a delirious and fainting condition. The first readings were taken from one-half to one hour after the race, but the pulse rate was so faint and the blood pressure so low that neither could be obtained. The average drop of the blood pressure after exercise was 24 mm.

In our study with the ergometer of the effect of exhaustive exercise on the circulatory reactions in normal schoolchildren, twelve of 110 children examined exceeded their limit of capacity in spite of all precautions taken. It was impossible by any methods to predict whether or not a child had reached the limit of its capacity. The circulatory reactions during exercise are not suggestive of overexertion. Thus, the opportunity presented itself to study sixteen cases of collapse in twelve children, thirteen occurring after exhaustive exercise on the ergometer and three, in two boys, after dumb-bell exercise. All of the children were perfectly normal, ranging high in weight, height and general muscular development. Three boys were 15 years old; three, 14; two, 13, and two, 12; and one was 11, and one, 9. The fact that there was a larger number of collapses in older children is probably to be laid to a greater spirit of competition. The subjective signs of collapse never occurred during exercise, but they became apparent after cessation of exercise, when practically all the boys were very dyspneic and covered with a profuse and general perspiration. Detailed information as to the technic was given in Part 1.

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[4] Potter, N. B., and Harrington, J. T.: Medical Supervision of Athletics Among Boys at Boarding School, J. A. M. A. **53**:1957-1960 (Dec. 11) 1909.

[5] Lowsley: The Effects of Various Forms of Exercise on Systolic, Diastolic and Pulse Pressures and Pulse Rate, Am. J. Physiol. **27**:446-466, 1911.

Every collapse manifested itself by nausea; in one case by vomiting. Two children complained of chills, and two others had a tremor of the entire body. In all subjects the heart sounds became so faint that they could scarcely be heard. In one child, a definite systolic murmur was audible at the apex for a period of five minutes; in another, a trigeminal extrasystole persisted until the blood pressure assumed the normal level. One child yawned continuously for about fifteen minutes after exercise. Fortunately, none of the children showed any untoward effects. Except for muscular fatigue, none showed any prolonged ill-effects. Only one child stayed away from school the following afternoon, all the others returning to their classes after a short period of rest. Race, physical development, height and weight had no bearing on the frequency of collapse. We were unable to detect clinical signs of acute dilatation, such as displacement of the apex beat to the left or an increase of the transverse diameter of the heart by percussion.

CIRCULATORY REACTIONS IN COLLAPSE RESULTING FROM EXHAUSTIVE EXERCISE

Blood Pressure.—The curves of the systolic blood pressure and pulse rate after cessation of exercise were so constant and striking that a detailed discussion of every case will be given. In every instance, the blood pressure dropped suddenly after cessation of exercise, the drop preceding nausea by from ten to 510 seconds. The subjective symptoms of collapse followed the objective circulatory signs. In nine of thirteen cases, the first exhibition of a sudden drop of blood pressure came within sixty seconds; in two, within two minutes, and in one, after five minutes. In all but two, the maximum rise was obtained on the first reading (in the majority of the cases at five seconds). In only three cases, the maximum rise occurred at ten, twenty and thirty seconds, respectively. In no instance did the blood pressure show a delayed rise. The maximum rise of blood pressure averaged 30 mm. In thirteen collapses, the blood pressure passed the preexercise level at an average of 155 seconds, the maximum being 330 seconds (Case 4) and the minimum twenty seconds (Case 12). The average difference between the preexercise level and the lowest subnormal reading was 16 mm., the highest subnormal reading being 40 mm. (Case 6), and the lowest 6 mm. (Case 3). These figures are not absolutely accurate because the readings had to be discontinued during the period of collapse. For the same reason, the reaction time of the blood pressure could be determined in only three cases. Case 8 had a reaction time of 720 seconds, Case 9 of 600 seconds and Case 7 of 420 seconds.

The foregoing circulatory reactions in collapse are in striking contrast to the circulatory reactions exhibited by the same children after exhaustive exercise without collapse. Here, the maximum rise of blood pressure occurred on an average at twenty-one seconds, and in only two at five seconds. The average maximum rise of the blood pressure was 36.2 mm. Only one big drop of the blood pressure occurred, usually at the time of severe perspiration, and never did the blood pressure drop below normal. The reaction time of the blood pressure in Case 8 was 330 seconds as against 720 seconds in collapse.

Table 1.—*Findings in Case 1 (M. F.)*

Pulse *			Blood Pressure	
Normal	Collapse	Time, Seconds	Collapse	Normal
...	180	5	149	...
156	180	10	...	166
168	...	20	...	163
156	156	30	152	161
...	156	40	149	...
...	148	50	148	...
144	132	60	130	150
132	132	90	130	154
132	132	120	124	154
126	126	150	119	134
120	126	180	111	133
120	132	210	110	133
108	Heart sounds faint	240	104	127
108	...	270	Nauseated, collapse	118
108	...	300	...	115
108	...	330	...	114
108	...	360	...	115
108	...	390	...	110
108	...	420	...	107
102	...	450	...	108
102	...	480	...	108
...	...	510	...	...
...	...	540	...	...
...	...	570	...	...
...	...	600	...	...

* Preexercise pulse rate, 90 beats; preexercise blood pressure : collapse, 110 mm.; normal, 108 mm.

Pulse Rate.—The drop of the pulse rate in collapse is not so striking as that of the blood pressure. In general, however, the pulse rate drops more suddenly in collapse than after exercise not followed by collapse.

REPORT OF CASES

Case 1 (Table 1).—M. F., aged 14, a perfectly normal boy, had had no previous experience in bicycle riding and at first had difficulty in riding smoothly. On his first attempt, he rode 13,842 foot pounds. Although he was markedly tired and dyspneic, the pulse and systolic blood pressure after cessation of exercise came back to normal by the usual decline. A few days later, he rode at the top of his speed, averaging about 225 revolutions per minute. He then rode 45,690 foot pounds in eleven minutes. He collapsed 240 seconds after cessation of exercise. The contrast between the curve in collapse and the one after severe exercise is very striking. Whereas in the normal curve[6] the heart could easily be heard, in the collapse the pulse became faint at 180 seconds and could not be counted even at the apex. The systolic blood pressure slowly descended after the ride of 13,842 foot pounds and returned to normal at 390 seconds; in collapse, however, it fell in jumps, the first drop being observed at ninety seconds (130 mm.) at which time, in the previous curve, it had reached only 159 mm. At 240 seconds, it had fallen to 104 mm., which is 6 mm. below normal. The readings had to be discontinued on account of nausea. When examined again at 480 seconds, the blood pressure had returned to the preexercise level, and the subject felt perfectly well.

Case 2 (Table 2).—H. P., aged 14, a slender boy, rode the bicycle twice. The blood pressure and pulse curves were normal after exercise of 20,730 foot pounds. He collapsed, however, after 22,176 foot pounds. Table 2 shows the difference in the blood pressure readings after the two experiments. In collapse, the blood pressure had dropped to 115 mm. at twenty seconds after cessation of exercise, as against 132 mm. in the other experiment. He complained of weakness; and he took a drink of water. After a second fall of the blood pressure, of 9 mm. at 120 seconds, the blood pressure descended slowly for 210 seconds, reaching the preexercise level at 300 seconds. In the following ninety seconds, it remained subnormal, the blood pressure having fallen 13 mm. below the normal reading. The boy was uncomfortable and felt nauseated, and the experiment was discontinued.

Table 2.—*Findings in Case 2 (H. P.)*

Pulse *			Blood Pressure	
Normal	Collapse	Time, Seconds	Collapse	Normal
...	168	5	130	...
168	156	10	132	...
156	...	20	115	132
156	144	30	115	126
...	144	40	Faint; water	
156	Heart sounds weak	50		126
156		60		126
144		90	114	117
132	126	120	105	110
132	126	150	105	103
132	126	180	101	103
132	...	210	96	99
132	126	240	99	93
132	...	270	99	93
...	126	300	92	...
...	...	330	82	...
120	126	360	81	...
...	126	390	80	...
...	Heart sounds faint	420	Collapse	...
...	...	450	...	...
...	...	480	...	...
...	...	510	...	...
108	...	540	...	...
...	...	570	...	...
...	...	600	...	...

* Preexercise pulse rate: collapse, 72 beats; normal, 81 beats; preexercise blood pressure, 93 mm.

Case 3 (Table 3 and Chart 1).—M. S., aged 12, was a sturdy boy of great endurance. The curves in Table 4 are typical of the circulatory reactions after exhaustive exercise and in collapse. The dotted lines represent the pulse and blood pressure curves after exercise of 25,452 foot pounds. No bad after-

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[6] For convenience, curves of circulatory reactions after severe exercise, not followed by collapse will be referred to as "normal curves."

TABLE 3.—*Findings in Case 3 (M. S.)*

Pulse *			Blood Pressure	
Normal	Collapse	Time, Seconds	Collapse	Normal
...	...	5	128	...
...	...	10	135	120
...	...	20	137	130
...	...	30	138	128
...	...	40	127	129
...	...	50	...	133
...	...	60	126	127
135	136	90	...	124
...	...	120	90	116
...	...	150	...	110
120	...	180	100	102
...	...	210	...	104
...	...	240	101	105
...	114	270	105	103
120	...	300	95	106
...	...	330	96	104
...	...	360	98	102
...	...	390	100	100
120	108	420	...	100
...	...	450	100	...
120	108	480	101	97
...	...	510	105	94
120	102	540	101	96
...	...	570	...	93
120	108	600	103	96

* Preexercise pulse rate, 88 beats; preexercise blood pressure: collapse, 101 mm.; normal, 97 mm.

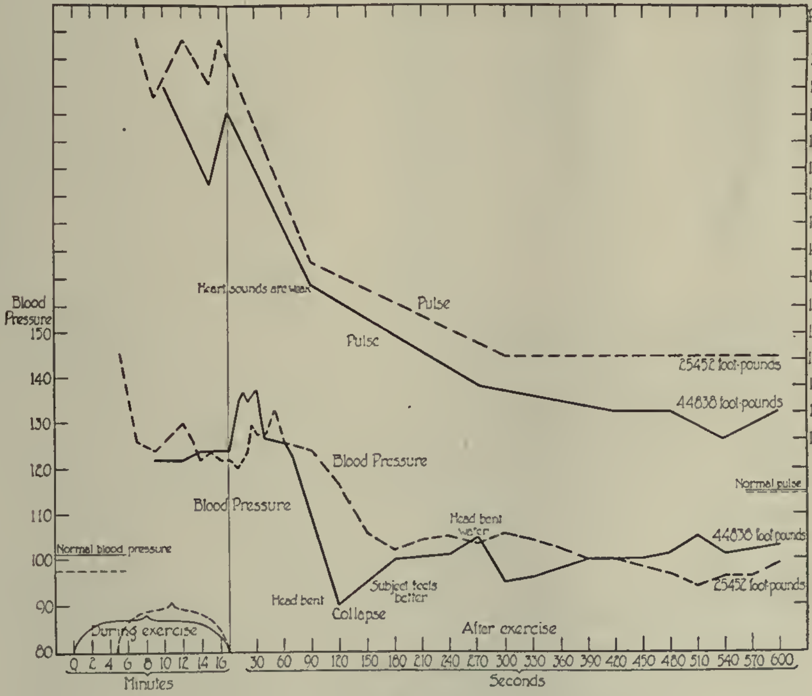

Chart 1.—Findings in Case 3 (M. S.).

effects resulted. The straight lines show the pulse and blood pressure descent in collapse, following exercise of 44,838 foot pounds. In the latter case, M. S. was in competition with another boy, this fact accounting for his greater exertion. The pulse rate drops more quickly in collapse, and the blood pressure exhibits a sudden fall (11 mm. below normal at 120 seconds). The subject was told to bend his head, a drink of water was given to him, and he felt better. The blood pressure rose 10 mm. to drop again 5 mm. below the preexercise level. The normal reading was finally maintained after 390 seconds. When taken off the bicycle, the boy complained of headache.

Case 4 (Table 4).—F. L., aged 14, a tall boy, felt perfectly well after exercising 24,952 foot pounds. He collapsed, however, after 16,260 foot pounds. In this experiment, signs of collapse did not manifest themselves until 360 seconds after cessation of exercise. At 420 seconds, the blood pressure had dropped 25 mm. below the preexercise level. When asked at 360 seconds whether he felt all right, he did not admit that he was ill; but one minute later he compained of severe nausea and therefore was taken off the bicycle. The circulatory reactions after exercise of 24,952 foot pounds were normal. In attempting to explain the discrepancy in Case 4, we found that the boy had a rhinitis and pharyngitis on the day that he rode 16,260 foot pounds, which explains the fact that he collapsed after a smaller amount of work.

Table 4.—*Findings in Case 4 (F. L.)*

Pulse *			Blood Pressure	
Normal	Collapse	Time, Seconds	Collapse	Normal
180	...	5	...	147
...	192	10	...	...
168	...	20	146	147
168	...	30	...	149
...	192	40	148	153
156	...	50	...	151
144	168	60	148	147
144	156	90	146	144
144	144	120	143	137
132	144	150	142	136
132	132	180	130	133
132	132	210	128	129
132	108	240	129	127
132	132	270	130	124
132	120	300	124	121
132	120	330	119	120
126	...	360	104	116
126	120	390	...	116
126	120	420	94	115
126	...	450	Collapse	113
132	...	480	...	113
...	...	510	...	...
132	...	540	...	...
...	...	570	...	...
...	...	600	...	...

* Preexercise pulse rate: collapse, 96 beats; normal, 102 beats; preexercise blood pressure: collapse, 119 mm.; normal, 110 mm.

Case 5 (Table 5).—H. G., aged 9, a well developed boy, collapsed after the first experiment, having accomplished 22,905 foot pounds on the bicycle. His blood pressure before exercise was 107 mm. and this level was passed at about 120 seconds after exercise. At 360 seconds, the blood pressure had dropped 15 mm. below normal, to rise to 101 mm. at from 420 to 450 seconds. The last audible reading was 94 mm. at 540 seconds. At 570 seconds, the blood pressure could not be heard at all. Collapse followed, and the child was taken off the bicycle. The blood pressure was still 93 mm. (15 below normal), while the pulse rate had reached its normal level.

Case 6 (Table 6 and Chart 2).—H. F., aged 15, and of splendid physique, of the 110 children examined for their maximum physical capacity on the ergometer, rode the longest and fastest (123,599 foot pounds). In a previous experiment, he had exercised 68,701 foot pounds, after which his circulatory reactions were normal, as can be seen from the dotted lines in Chart 2. Six minutes after the ride of 123,599 foot pounds, however, he completely collapsed. The blood pressure and pulse curves obtained in this instance are typical collapse curves; the continuous precipitate drop of the blood pressure, the sub-

Table 5.—*Findings in Case 5 (H. G.)*

Pulse *			Blood Pressure	
Normal	Collapse	Time, Seconds	Collapse	Normal
...	...	5	122	130
...	...	10	128	127
...	...	20	118	127
...	...	30	116	127
...	...	40	115	123
...	...	50	111	...
...	...	60	111	122
144	...	90	116	118
...	...	120	107	113
132	...	150	98	112
...	72	180	...	109
138	...	210	98	111
132	144	240	99	107
...	...	270	...	109
...	144	300	...	107
...	...	330	94	105
132	..	360	92	105
...	138	390	...	...
144	...	420	...	100
138	...	450	101	100
...	126	480	101	101
126	138	510	...	101
...	...	540	94	101
132	...	570	Not audible,	100
...	144	600	collapse	102

* Preexercise pulse rate: collapse, 107 beats; normal, 96 beats; preexercise blood pressure, 107 mm.

Table 6.—*Findings in Case 6 (H. F.)*

Pulse *			Blood Pressure	
Normal	Collapse	Time, Seconds	Collapse	Normal
192	192	5	142	...
...	192	10	...	...
...	...	20	...	150
...	156	30	129	...
...	144	40	118	150
...	...	50	118	...
120	138	60	120	150
120	120	90	112	147
108	132	120	105	140
120	120	150	94–85	132
120	120	180	90	127
120	120	210	89	122
120	...	240	Felt faint	119
108	108	270	90	115
108	108	300	90	117
...		330	85; 74	114
...		360	Nauseated, collapse	...
...	Heart sounds dull	290	..	...
...		420	...	...
...		450	...	...
...		480	...	...
...	108	510	...	...
...	102	540	...	...
...	96	570	...	...
...	96	600	...	...

* Preexercise pulse rate: collapse, 84 beats; normal, 96 beats; preexercise blood pressure, collapse, 114 mm.; normal, 118 mm.

normal phase (40 mm. below normal, the highest subnormal reading obtained in our experiments). The curve to the left of the dividing line, representing the blood pressure readings during exercise, is typical in its slight ascent immediately after the beginning of exercise, forming practically a straight line thereafter throughout the experiment. Typical for collapse is the sudden drop of blood pressure at cessation of exercise, instead of a slight increase of the blood pressure during the first thirty seconds following cessation of work, as is usually the case.

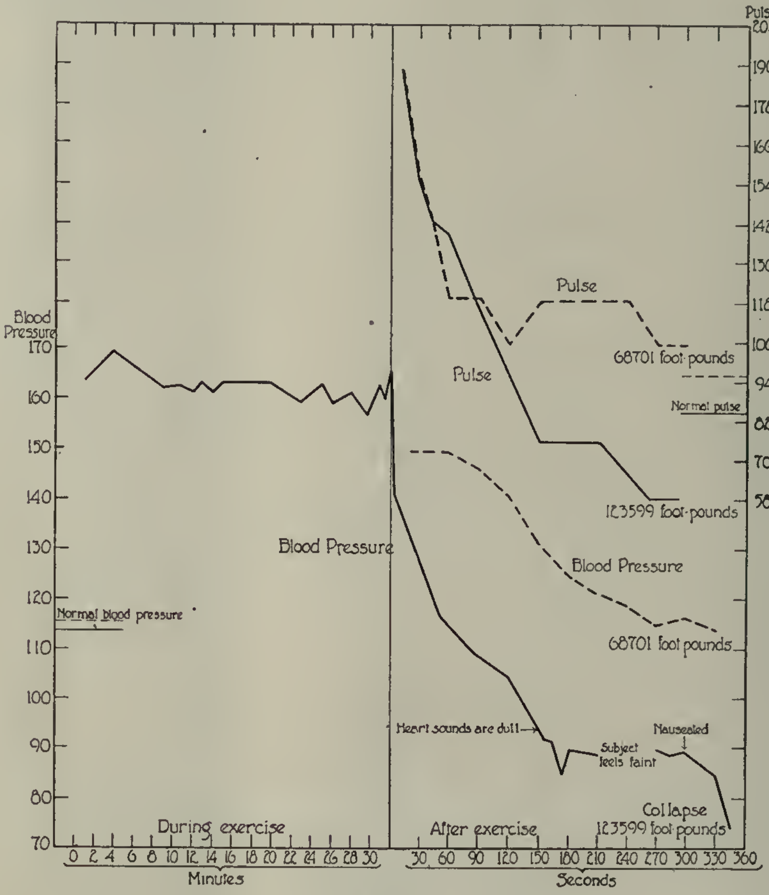

Chart 2.—Findings in Case 6 (H. F.).

Case 7 (Table 7 and Chart 3).—A. P., aged 13, exhibited a normal course of the circulatory reactions after exercise of 69,354 foot pounds. On repeating the experiment, he was able to ride for but nine minutes, performing 37,040 foot pounds. The maximum rise of the blood pressure in the latter experiment was 28 mm. at five seconds. The blood pressure soon dropped to 119 mm. (at fifty seconds), and reached the preexercise level at about ninety seconds. At 180 seconds, the blood pressure had fallen 19 mm. below normal. The boy complained of nausea and dizziness, and was therefore allowed to lie down. The subsequent readings were taken in the supine posture. Allowing for a difference of 10 mm. between the readings in the lying and standing

TABLE 7.—*Findings in Case 7 (A. P.)*

Pulse *			Blood Pressure		
Normal	Collapse	Time, Seconds	Collapse		Normal
...	180	5	140		...
180	168	10	140		146
180	156	20	...		...
...	...	30	137		...
168	156	40	...		144
...	156	50	119		...
168	...	60	...		143
144	144	90	111		132
144	144	120	110		130
144	144	150	109		124
144	132	180	93		124
132	132	210	Collapse		125
132	...	240	111	Taken lying	120
138	...	270	107		119
132	...	300	115		118
132	...	330	115		120
132	...	360	117		118
120	...	390	122		116
132	...	420	...		115
126	...	450	...		116
120	...	480	120		114
...	...	510	...		...
...	...	540	...		...
...	...	570	...		...
...	...	600	...		...

* Preexercise pulse rate: collapse, 80 beats; normal, 108 beats; preexercise blood pressure, collapse, 112 mm.; normal, 114 mm.

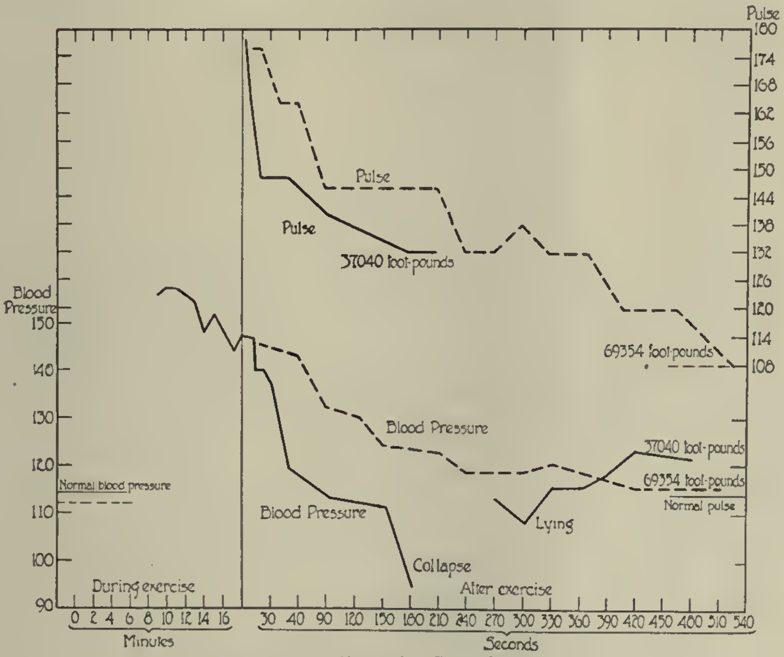

Chart 3.—Findings in Case 7 (A. P.).

Table 8.—*Findings in Case 8 (I. B.)*

Pulse *				Blood Pressure		
Normal 2	Normal 1	Collapse	Time, Seconds	Collapse	Normal 1	Normal 2
192	...	168	5	152	...	150
180	168	...	10	152	127	149
168	168	156	20	141	134	152
156	156	...	30	138	133	154
156	156	132	40	137	136	152
156	156	...	50	130	...	155
144	156	132	60	120	136	159
138	...	...	90	...	133	150
126	144	...	120	117	135	145
126	138	108	150	115	130	138
126	138	108	180	Collapse	129	129
126	132	...	210	...	126	133
126	132	...	240	...	120	127
126	144	..	270	...	...	121
126	126	116	300	120	130	129
126	132	...	330	...	129	125
126	132	...	360	...	124	127
120	132	...	390	...	124	127
120	132	...	420	...	119	127
120	132	...	450	...	119	127
120	132	..	480	...	119	...
120	126	...	510	..	119	119
...	126	...	540	...	119	...
...	126	...	570	...	118	...
...	126	...	600	...	119	...

* Preexercise pulse rate, 96 beats; preexercise blood pressure: collapse, 130 mm.; normal, 124 mm.

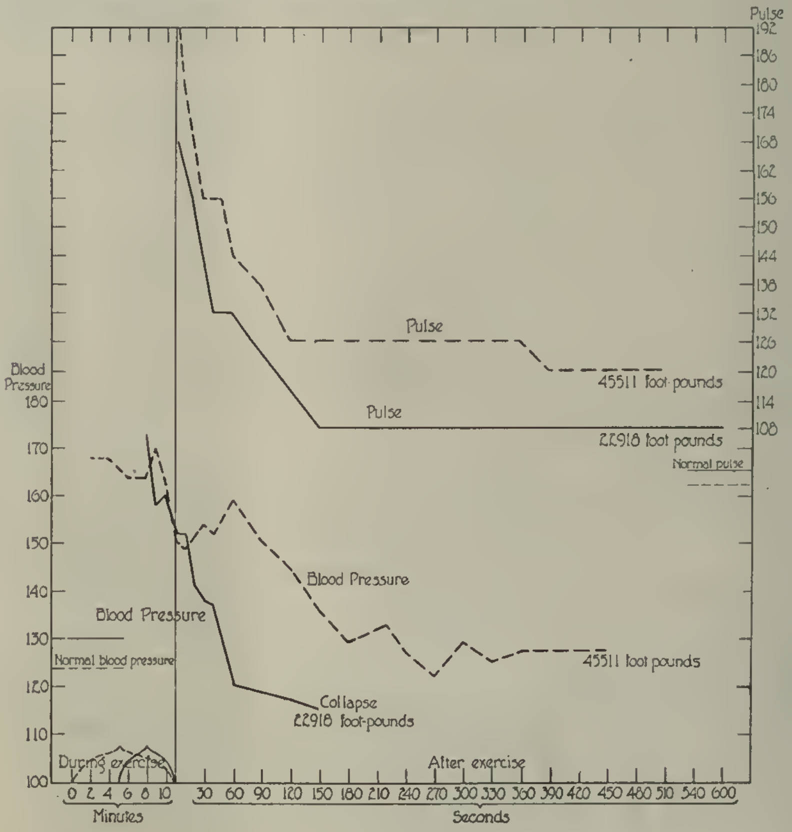

Chart 4.—Findings in Case 8 (I. B.).

position in favor of the lying position, these figures would indicate a return of the blood pressure to normal at about 420 seconds. The boy admitted after the experiment that he was suffering from a sore throat. This may have been the cause of the collapse resulting after only 60 per cent. of the work he was able to perform on a previous occasion without untoward effects. He stayed away from school in the afternoon, and returned in good physical condition the next morning.

Case 8 (Table 8 and Chart 4).—I. B., aged 14, a strong and sturdy boy, who rode the bicycle three times, performed 46,705 foot pounds the first time (Table 8, under Normal 2). The blood pressure curve as well as the pulse curve after cessation of exercise are normal. He developed a murmur at forty seconds. The reaction time was 420 seconds. A month later, on riding the bicycle again, he was able to do 45,511 foot pounds (Table 8, under Normal 1) Except for fatigue, he did not complain of any symptoms of overexertion. The circulatory reactions after exercise were the usual ones. The reaction time of the blood pressure was 360 seconds. A week later, he rode the bicycle for the third time. After five minutes' exercise, he asserted that he was unable to continue. He had accomplished only 22,918 foot pounds. The exercise was discontinued, and the circulatory reactions were tested. Typical collapse curves were presented. There was a precipitate drop of the blood pressure, reaching the preexercise level at fifty seconds, and a subnormal phase (from fifty to 150 seconds; the normal blood pressure equaled 130 mm.). The blood pressure could not be observed between 150 seconds (time of collapse) and 270 seconds. A reading taken twelve minutes after cessation of work gave the blood pressure as 117 mm., 13 mm. below the preexercise level. Chart 4 presents fully the circulatory reactions in collapse of subject I. B. His lowered physical capacity was due to a cold (cough), as admitted afterwards.

Table 9.—*Findings in Case 9 (E. B.)*

Pulse *			Blood Pressure	
Collapse 2	Collapse 1	Time, Seconds	Collapse 1	Collapse 2
192	...	5	...	156
180	192	10	...	155
...	...	20	142	153
168	168	30	140	152
156	168	40	...	144
...	...	50	. .	134
144	156	60	...	132
144	...	90	118	132
132	120	120	103	115
132	Heart sounds faint	150	Collapse	104
132		180	...	105
132		210	...	101
126		240	...	103
126		270	...	103
126	96	300	. .	102
120	...	330	...	Collapse
120	...	360	. .	109
116	...	390	...	108
114	...	420	. .	109
114	...	450	...	110
114	...	480	. .	114
114	. .	510	...	106
...	. .	540	...	...
106	...	570	...	104
106	. .	600	...	100
106	...	13 min.	...	112

* Preexercise pulse rate: collapse 1, 96 beats; collapse 2, 90 beats; preexercise blood pressure: collapse 1, 111 mm.; collapse 2, 113 mm.

Case 9 (Table 9).—E. B., aged 15, one of the athletes of the school, who rode the bicycle twice, collapsing each time, in the first experiment rode for twenty-two minutes at a speed of 277 revolutions per minute, performing 101,260 foot pounds. The pulse rate as well as the blood pressure fell precipitately after cessation of work, the former reaching the preexercise level at 300 seconds (an abnormal occurrence); the latter falling 8 mm. below normal at 120 seconds. The readings had to be discontinued on account of collapse. Five weeks later, he insisted on riding the bicycle again in order to outdo H. F. He stopped, however, after nine minutes, having performed but 40,811 foot pounds (as was learned later, he had a cough, and hoarse voice). Here again we find the subnormal phase, with 101 mm. (12 mm. below normal). He felt nauseated and faint at 120 seconds, when the blood pressure had fallen 17 mm. The readings had to be discontinued from 300 to 330 seconds on account of collapse. The last blood pressure taken was 112 mm. (preexercise level) at thirteen minutes.

Case 10 (Table 10).—D. F., aged 15, of strong constitution, performed 108,762 foot pounds in twenty-four minutes and thirty seconds, without any complaint of ill effects. The circulatory reactions after cessation of exercise were normal. Two weeks later, running a race with H. F., he rode for twenty-seven minutes, at a lower speed, however, than in the previous experiment, thus bringing his work to but 106,208 foot pounds. After exercise of 108,762 foot pounds, the maximum blood pressure rise was 33 mm.; after 106,208 foot pounds, practically the same amount of work, only 25 mm. While in the first experiment the blood pressure was still 21 mm. above normal at 120 seconds, it had already dropped to 109 mm. (18 mm. above normal) in collapse. While in the former the blood pressure maintained itself at the preexercise level from 240 seconds on, in the latter it passed this level at 240 seconds. The boy felt sick at 330 seconds, so that the readings had to be discontinued for the time being. The maximum fall was observed at 480 seconds (11 mm. below normal). No further readings were taken on account of nausea.

Table 10.—*Findings in Case 10 (D. F.)*

Pulse *			Blood Pressure	
Normal	Collapse	Time, Seconds	Collapse	Normal
192	180	5	126	142
...	180	10	...	146
180	...	20	...	144
168	...	30	122	143
...	168	40	118	140
156	144	50	...	143
144	144	60	118	141
144	132	90	117	138
144	132	120	109	134
132	132	150	106	128
144	132	180	104	120
132	132	210	102	122
120	120	240	99	114
132	120	270	96	114
132	112	300	96	113
...	120	330	...	113
...	...	360	...	114
...	...	390	...	112
...	112	420	100	...
...	...	450	98	...
...	...	480	90	...
...	...	510	...	...
...	...	540	Nauseated	...
...	...	570	...	...
...	...	600	108	...

* Preexercise pulse rate: collapse, 90 beats; normal, 96 beats; preexercise blood pressure: collapse, 101 mm.; normal, 113 mm.

Case 11 (Table 11).—R. B., aged 12, brother of E. B., collapsed after exercising 49,754 foot pounds. The lowest blood pressure reading after cessation of exercise was 19 mm. below the preexercise level. He felt so weak that the blood pressure cuff had to be removed.

Case 12 (Table 12).—A. G., aged 12, a healthy, well developed boy, brother of H. G., collapsed in the first experiment (36,248 foot pounds). The first blood pressure reading obtained after cessation of exercise was 119 mm. at twenty seconds (preexercise reading). The blood pressure had already dropped 28 mm. at 150 seconds, when the readings had to be discontinued because of vomiting. The following week, on repeating the experiment, he performed 33,831 foot pounds. The circulatory reactions in this experiment were slightly irregular, as can be seen in Table 12. This may be due to the fact that he was allowed to drink water and to bend his head to avoid collapse.

Table 11.—*Findings in Case 11 (R. B.)*

Pulse *			Blood Pressure	
Normal	Collapse	Time, Seconds	Collapse	Normal
...	...	5	..	...
...	...	10	...	...
...	...	20	...	...
...	...	30	...	...
168	...	40	...	147
144	...	50	107	151
...	...	60	99	...
144	...	90	...	146
...	...	120	100	...
144	...	150	87	146
156	...	180	...	142
144	...	210	Collapse	137
144	...	240	...	129
144	...	270	...	124
126	...	300	...	124
114	...	330	...	118
120	...	360	...	...
120	...	390	...	...

* Preexercise pulse rate, 108 beats; preexercise blood pressure, collapse, 106 mm.

Table 12.—*Findings in Case 12 (A. G.)*

Pulse *			Blood Pressure	
Normal	Collapse	Time, Seconds	Collapse	Normal
...	...	5	...	137
...	...	10	...	132
...	...	20	119	129
...	...	30	119	135
...	...	40	104	124
...	...	50	113	119
...	...	60	116	119
...	...	90	109	105
...	...	120	109	113
...	...	150	91	...
...	...	180	...	121
...	...	210	...	115
120	...	240	...	115
...	...	270	...	114
...	...	300	...	111
102	...	330	...	112
108	...	360	...	107
...	...	390	...	102
102	...	420	...	111
...	...	450	...	101
...	...	480	...	107
...	...	510	...	...
...	...	540	...	109
...	...	570	...	113
...	...	600	...	113

* Preexercise pulse rate, 87 beats; preexercise blood pressure: collapse, 119 mm.; normal, 110 mm.

COLLAPSE AFTER DUMBBELL EXERCISE

Case 13 (*a* and *b*).—R. T., aged 13, collapsed after having swung two 4-pound dumbbells from the floor the full arm length 120 times (*a*) and 110 times, (*b*) respectively. He was very dyspneic after the exertion. The circulatory reactions confirmed the findings on the ergometer in the cases of collapse after exercise. After 120 swings, the blood pressure had risen 5 mm. at ten seconds, to fall 7 mm. below normal at fifty seconds, 28 mm. at 140 seconds, and 44 mm. at 180 seconds. The heart sounds became faint. The readings had to be discontinued on account of great distress. After a short rest, a reading was taken at the end of five minutes, with the boy lying on his back. The blood pressure had returned to normal. Two weeks later, he was asked to swing the dumbbells 110 times. The maximum blood pressure reading after exercise was obtained at forty seconds (14 mm. above normal). The blood pressure curve after exercise took practically the usual course for 150 seconds, reaching the preexercise level at 130 seconds. At 155 seconds, the blood pressure showed a sudden drop of 7 mm. below normal, falling as low as 47 mm. below normal at 310 seconds. The fall in the blood pressure coincided with the physical discomfort experienced by R. T. from 155 seconds on. The readings were discontinued at 310 seconds, on account of nausea.

Case 14.—C. T., aged 13, a fat boy, had swung two 4-pound dumbbells 100 times without ill effect. The percentage of recovery of the blood pressure at 180 seconds was 92.8; that of the pulse rate, 76.5. Two weeks later, the boy was told to swing two 4-pound dumbbells but thirty-five times. He vomited, 240 seconds after cessation of work. The blood pressure had reached the preexercise level at 120 seconds and had fallen 28 mm. below normal at 180 seconds. The highest drop was obtained at 240 seconds (39 mm.), at which time he vomited. The blood pressure was still 20 mm. below normal, five minutes and thirty seconds after cessation of exercise. When questioned about his physical condition, the boy admitted that he had been suffering from a headache that day and that he felt very tired from playing football during the two weeks of Thanksgiving vacation.

COMMENT

The physiology of muscular exercise is highly complicated. Not only the muscles of the body, but also the heart muscle, the vagus nerve, the vasomotor system, the heat regulating apparatus, the lungs and even the central nervous system are all mobilized in muscular activity. In all of our cases of collapse, two striking facts were observed: 1. Subjective signs resulting from exhaustive exercise simulating those in shock. This suggests a sudden anemia of the brain. 2. A marked drop in the systolic blood pressure and the pulse rate after cessation of exercise in every collapse.

The explanation of the curves obtained must be sought in the cause of the sudden lowering of the blood pressure and the pulse rate. 1. Is the fall of the blood pressure and the pulse rate due to an overstretching of the heart muscle beyond the physiologic limits? At the beginning of exercise, the muscles used squeeze the blood into the veins of the muscles, thus causing an increase of venous pressure. The heart muscle must then dilate in order to accommodate the increased amount of blood received. This dilatation depends on the physiologic condition of the heart muscle, the momentary length of the fibers and the thickness of the walls. The opinion that dilatation of the heart occurs in a normal person during severe exercise was advanced by many great clinicians. They claimed to have found, by percussion, an increase in the transverse diameter of the heart, and a displacement of the heart apex to the left and downward. Schott held the same view, at first through clinical observations, later confirming it by roentgen-ray studies after exercise.[7] Schott's work is open to criticism because the size of the heart was not observed during exercise. In recent years, the opinion has gained ground that, in a normal person, even during and after most exhaustive exercise, the diastolic volume of the heart does not increase. Hoffman (1902), De La Camp[8] (1902), Moritz[9] (1908) and Williamson[10] (1911) found by means of the orthodiagraph that, in healthy people, severe exercise to the point of exhaustion produced no increase in the transverse diameter of the heart; moreover, the transverse diameter actually decreased. In 1914, Nicolai and Zuntz[11] stated that there was a small increase of the transverse diameter of the heart, averaging 4 mm. during exercise, followed within three seconds after cessation of exercise by a definite decrease. In Williamson's experiments, twenty-nine of a series of thirty-two subjects exhibited a smaller heart after exercise, only three subjects showing an increase in heart size.

In our experiments, there is no evidence for the theory that an acute dilatation of the myocardium is the cause of collapse in normal children. In every case, the apex beat was in its normal position; the transverse diameter of the heart was not increased; the subjective signs described above disappeared in a very short time after cessation of exercise, and the child resumed his school work in a normal condition.

Whether or not these curves can be explained on the basis of a disturbance of the function of the vasomotor system, as is the case in shock, will be more fully considered in the next paper, Part 3 of this series: Roentgen-Ray Studies in Collapse.

SUMMARY AND CONCLUSIONS

1. The circulatory reactions following exhaustive exercise resulting in collapse were studied on fourteen normal boys of school age.
2. In collapse, the curves of the blood pressure and pulse rate after exercise assume the same character in every instance.
3. Race, physical development, height and weight have no bearing on the frequency of collapse.

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[7] Schott: Zur acuten Ueberanstrengung des Herzens und deren Behandlung, Verhandl. d. IX Cong. f. inn. Med. zu Wien. **9**:448-477, 1890.

[8] De la Camp, O.: Experimentelle Studien über die acute Herzdilation, Ztschr. f. klin. Med. **51**:1-79, 1903-1904.

[9] Dietlin and Moritz: Ueber das Verhalten des Herzens nach langandauerndem und ansterengendem Radfahren, München. med. Wchnschr. **55**:489-492, 1908.

[10] Williamson, C. S.: Functional Testing of Cardiac Power, Lancet-Clinic **111**:201-206, 1914.

[11] Nicolai and Zuntz: Füllung und Entleerung des Herzens bei Ruhe und Arbeit, Berl. klin. Wchnschr. **51**:821-824, 1914.

4. In no instance did signs of collapse occur during exercise.

5. In all but two cases, the maximum rise of blood pressure occurred at the first reading (within the first ten seconds) after exercise.

6. No delayed rises were obtained after exercise.

7. The maximum rise of blood pressure after cessation of exercise averaged 30 mm.

8. In sixteen collapses, the blood pressure passed the preexercise level on an average of 127 seconds (with a maximum of 150 seconds in the case of R. T. [*b*], and a minimum of 35 seconds [R. T., *a*]).

9. The curve of the pulse rate after exercise runs parallel with the curve of the blood pressure, although the drop is not so marked.

CALCIUM AND PHOSPHORUS DETERMINATIONS IN THE BLOOD PLASMA IN RICKETS AND TETANY *

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Primarily, three groups of cases were selected for blood studies: cases (1) of milk rickets; (2) of typical severe rickets, and (3) of active tetany showing rachitic changes. The cases covered prematurely born, full-term, breast-fed and artificially fed infants. The majority of the infants were between 4 and 12 months of age. The calcium and inorganic phosphorus content of the blood plasma was determined before treatment, and in some cases after treatment. The studies were started with a possibility in mind that rickets might be classified into low phosphorus and low calcium groups, and a third intermediate group; and that certain clinical manifestations might be anticipated by a study of the blood in infants.

Howland and Kramer[1] determined the inorganic phosphate of the serum in a series of normal children. They found the concentration to average 5.4 mg. per hundred cubic centimeters, with a minimum of 4 mg. and a maximum of 7.1 mg., the higher values usually being found in the serum of exclusively breast-fed children.

Kramer and Tisdall[2] give the average values of calcium found in normal infants as 10.5 mg. per hundred cubic centimeters of serum. These figures agree with those of other investigators.

Howland and Kramer[3] state that a study of the calcium and phosphorus of the serum in children with rickets and with rickets complicated by tetany leads them to believe that the determining factor in the calcification of the bones is the presence of calcium and phosphorus in

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[1] Howland, John, and Kramer, Benjamin: Calcium and Phosphorus in Serum in Relation to Rickets, Am. J. Dis. Child. **22**:105 (Aug.) 1921.

[2] Kramer, Benjamin, and Tisdall, F. F.: J. Biol. Chem. **47**:475 (Aug.) 1921.

[3] Howland, John, and Kramer, Benjamin: Tr. Am. Pediat. Soc. **34**:204, 1922. Briggs, A. P.: J. Biol. Chem. **53**:13 (July) 1922 (a modification of the Bell-Doisy method). Kramer, Benjamin, and Tisdall, F. F.: A Simple Technic for the Determination of Calcium and Magnesium in Small Amounts of Serum, J. Biol. Chem. **47**:475 (Aug.) 1921.

such amounts that the product of their concentration in milligrams per hundred cubic centimeters of serum equals a certain minimal figure, which ranges from 30 to 40. In rickets, they found that the concentration of calcium in the majority of instances is essentially normal; whereas, the phosphorus concentration varies from 0.8 to 3.4 mg. With tetany, on the other hand, the inorganic phosphorus usually approaches normal, varying from 3.6 to 5.8 mg. per hundred cubic centimeters of serum; while the calcium is distinctly lowered. The product of the calcium and phosphorus concentration usually varies from 24 to 31, the low product in tetany being due, in the majority of instances, to a diminution of the calcium concentration. It will be seen that the product in tetany is higher than it is in the many uncomplicated cases of rickets. In other words, it is nearer the healing point, and this is in line with the experience that the evidences of rickets in patients with tetany are not usually of a high grade.

Shipley, Park, McCollum and Simmonds[4] believe that there are two chief types of rickets: one characterized by a normal or nearly normal blood calcium and a low phosphorus (low phosphorus rickets); and the other, by a normal or nearly normal blood phosphorus but a low blood calcium (low calcium rickets). These authors base their views on the experimental production of rickets in rats by various alterations in the diets.

These authors state: "As is well known, tetany complicates certain cases of rickets, but not by any means all. Cases of rickets, even very severe, exist, in which tetany does not supervene. It is with the less severe forms of rickets that tetany usually allies itself." They found that, in some cases of rickets accompanied by tetany, the roentgen ray shows a deposition of lime salts at the cartilage-shaft junctions of the long bones of the extremities; apparently cases of healing rickets. They believe the reason for this is, in many instances, this:

> In the low calcium and the low phosphorus forms of rickets, calcium-phosphate ratios exist in the blood which do not permit at all or permit to only a very limited extent the deposition of calcium and phosphate in the bones. Between the low calcium form of the disease and the normal condition, on the one hand, and the low phosphorus form and the normal condition on the other, are innumerable gradations, presumably characterized by calcium-phosphate ratios in the blood, very probably oscillating ratios which permit calcium phosphate deposition in varying degree, from the most fragmentary to almost complete calcification. In connection with both the low calcium and the low phosphorus forms of rickets, therefore, there are borderline states of the disease in which the calcium-phosphate ratios are such as to permit calcium phosphate deposition to take place irregularly or intermittently in the bones.
>
> According to present knowledge, the relationship between tetany and rickets appears to be as follows: Tetany is an expression on the part of the nervous

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[4] Shipley, P. G.; Park, E. A.; McCollum, E. V., and Simmonds, Nina: Is There More Than One Kind of Rickets? Am. J. Dis. Child. **23**:91 (Feb.) 1922.

tissues of an insufficiency of the calcium ion; rickets is an expression on the part of the skeleton of disturbed relations between the calcium and phosphate ions of the body fluids. The reason that tetany is so frequently associated with rickets is because rickets is a disease in which the calcium ion in the body tissues and fluids is subject to wide variations. Tetany occurs independently of rickets just as rickets occurs independently of tetany. Since tetany may occur with the low phosphorus form of rickets, it does not serve to mark off one form of rickets from the other. Tetany is essentially associated, however, with the low calcium form of rickets and, for all practical purposes, the low calcium form is the rickets of tetany.

Another interpretation of tetany is that of György, who believes that, notwithstanding the fact that the phosphorus values are rarely above normal, one can speak of a relative phosphorus stasis, and, further, that a phosphate impoverishment of the blood prevails in rickets, while a relative phosphate congestion is found in tetany. György[5] further states that the amount of calcium ions in the serum depends less on the total calcium than on the other ions dissolved in the serum. An increase in the bicarbonate and phosphate, as well as a reduction of the hydrogen ion concentration, produces a reduction of the calcium ions and therefore acts to produce a tetany. These changes indicate an alkalosis of the blood.

Freudenberg and György[6] and Rona and Takahashi[7] believe that there is a tendency to alkalosis in manifest tetany; that calcium ion concentration is directly proportionate to hydrogen ion concentration and inversely proportional to bicarbonate content. They contend that phosphates and bicarbonates may be placed in the same categories—increased phosphorus content tends to diminish calcium ionization. The alkalosis may be neutralized, phosphate diuresis begun and the tetany cured by the administration of hydrochloric acid or of other substances producing an increase of this acid in the body, such as ammonium chlorid and calcium chlorid.

Freudenberg and Aschenheim[8] interpret rickets from a similar standpoint. They found that the blood in rickets is poorer in inorganic phosphate and that the urine of rachitic infants contains more phosphate and excessive amounts of ammonia, both of which are signs of acidosis. The acidosis reduces the phosphate content of the blood as a result of the increased excretion of phosphate in the urine and leads to marked mobilization of calcium, so that the calcium content of the blood remains normal in spite of a protracted loss of calcium; and, in this way, produces an abnormal composition of ions in the blood plasma.

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[5] György, P.: Klin. Wchnschr. **69**:1399 (July 8) 1922.

[6] Freudenberg, E., and György, P.: München. med. Wchnschr. **69**:422 (March 24) 1922; Jahrb. f. Kinderh. **100**:86, 1922.

[7] Rona and Takahashi, quoted from György, P.: Jahrb. f. Kinderh. **99**:1, 1922.

[8] Freudenberg, E.: Klin. Wchnschr. **1**:1422 (July 8) 1922. Aschenheim, Eric: Deutsch. med. Wchnschr. **49**:85 (Jan. 19) 1923.

Huldschinsky [9] concludes that tetany is usually associated with the healing stage of rickets and that it is due to the withdrawal of calcium from the body tissues at the time the calcification of the bone is taking place.

MODERATE RICKETS

In a group of eight cases of moderate rickets, we found that the phosphorus was either normal or moderately reduced. Two of these patients had received some breast milk from birth. The calcium in these was normal. In those receiving cow's milk mixtures from birth, there was a moderate calcium reduction. In all of the cases, except one, the product of the milligrams of phosphorus and calcium per hundred cubic centimeters of plasma was over 40.

Table 1.—*Moderate Rickets*

Patient	Sex*	Age, Months	Weight		Race†	Diet	P, Mg. per Hundred C.c.	Ca, Mg. per Hundred C.c.	Remarks
			Lbs.	Oz.					
C. B.	♂	7½	9	12	W	Breast and milk mixture from birth	5.4	13.00	Premature; congenital heart thymus; spastic apnea
J. H.	♀	5½	14	..	W	Breast and milk mixture for 4 months	5.56	11.27	Slight rickets
F. R.	♂	7	15	..	W	Breast fed 4 weeks; milk mixture 6 months	4.0	10.35	Little's disease; convulsions since birth
S.	..	3½	12	8	W	Milk mixture from birth	5.23	9.31	
W. B.	♂	4	10	..	W	Milk mixture from birth	4.76	7.54	Spastic paralysis
N. L.	♂	4	13	..	W	Milk mixture	4.76	9.09	
D. B.	♀	13	12	12	W	Milk mixture from birth	3.22	9.40	Full term; microcephalus
A. B.	♂	10	14	..	C	....	4.50	10.19	

* In this column, ♀ indicates female; ♂, male.
† In the tables, W = white; C = colored.

SEVERE RICKETS

In a group of seventeen cases of severe rickets, all except one case had a phosphorus content below 2.7, ranging as low as 1.35. In the one exception, in an infant, aged 6 months, who had received part breast-feeding from birth, there was a phosphorus content of 3.82. The calcium was normal or only slightly reduced in thirteen cases; while in the remaining four (all in colored infants), the amounts ranged from 6.73 to 8.92. The product in all these cases was under 30, and ranged as low as 9. Two of the patients still presenting all the clinical evidence of severe rickets, but roentgenologic evidence of healing, after two and three months, respectively, on cod liver oil showed a phosphorus and calcium product in the first case of 53, in contrast to a former content of 13.5; and in the second case, a content of 65. Two of the patients, both aged 10 months, presented cases which were complicated by acute severe scurvy. They had, with one exception, the lowest phosphorus values of the group: 1.43 and 1.53; while their plasma calcium content was approximately normal. Two cases of congenital syphilis were among the group, the ages of the patients being 11 and 10 months. The complicating syphilis apparently made no difference as compared with other cases showing the same degree of rickets. In several cases in which there had been repeated convulsions, with congenital syphilis and birth hemorrhages as a basis, but in which there was no evidence of tetany, calcium values were approximately normal. One case of osteopsathyrosis with multiple fractures had a phosphorus content of 2.12 and a calcium of 11.45 after six weeks of treatment with cod liver oil.

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[9] Huldschinsky, K.: Ztschr. f. Kinderh. **26**:5, 207, 1920.

TABLE 2.—*Severe Rickets*

Patient	Sex*	Age, Months	Weight		Race†	Diet	P, Mg. per Hundred C.c.	Ca, Mg. per Hundred C.c.	Remarks
			Lbs.	Oz.					
J. F.	♂	10	8	11	W	Milk mixture from birth	1.43	9.45	Severe scurvy; blood taken March 5
		12	..	..	W	Milk mixture from birth	4.93	10.10	Healed scurvy; blood taken May 8; cod liver oil, 1 tsp. twice a day; orange juice, 1 ounce daily for 2 months
J. P.	♂	10	12	..	W	Milk mixture	1.53	11.53	Severe scurvy
M. M.	♀	8	9	5	W	Milk mixture	2.42	11.99	Premature
E. T.	♂	8	8	8	W	Milk mixture	5.80	11.30	Premature; cod liver oil 3 months
C. F.	♂	17	20	..	C	Breast fed 2 months	1.35	6.73	No cod liver oil
R. A.	♂	11	17	..	W	Breast fed 2 months	2.38	12.17	Congenital syphilis; repeated convulsions from birth
E. S.	♀	6	9	..	C	Eagle brand milk	2.08	10.90	Serum in this case showed: P, 2.5; Ca, 13.1
G. S.	♀	10	12	..	C	Milk mixture	2.00	7.30	No cod liver oil; congenital syphilis
L. R.	♂	8	16	..	C	Breast and milk bixture	2.22	10.72	
A. B.	♂	7	11	..	C	Milk mixture	2.66	10.09	
S.	..	36	..	..	C	Milk mixture	2.10	12.90	
H. G.	♀	9	14	..	C	Breast fed 7 months	2.12	10.78	COC, 10+
H. A.	♂	19	..	..	C	Breast fed 11 months	2.15	8.92	
L.	..	16	..	..	C	Breast fed 1 year	2.12	9.40	Full term; COC, 10+
B. A.	..	..	..	..	C	.............,	2.37	7.05	
E. W.	♂	14	15	..	C	Milk mixture from birth	2.12	11.45	Osteopsathyrosis; multiple fractures
J. C.	♂	6	13	8	W	Breast and milk mixture from birth	3.82	10.10	

* In this column, ♀ indicates female; ♂, male.

To summarize, regarding moderate and severe rickets:

1. Clinical signs are of great value in determining the degree of rickets. They are, however, of very little value in differentiating between the active and inactive phases of the disorder.

2. Repeated roentgenologic studies are more important in establishing the active and healing stages.

3. Consecutive blood examinations to determine the phosphorus-calcium concentration and their ratios and products are most important in the diagnosis of the degree and stage of rickets and the prognostication of probable complications.

Definite diagnosis, however, should be based on the three findings mentioned, with relative consideration to past and present diet, environment, season, acute infections and medicinal and physical therapy, since these factors are sufficient in themselves to change, not only the blood findings, but the clinical manifestations as well.

It is believed that calcium and phosphorus concentration with a minimal product between 30 and 40 is the determining factor in the calcification of bones.

All cases of rickets with a calcium and phosphorus content of less than 30 must be considered as in the active zone. The low phosphorus is usually the factor influencing the low product, but this may also be caused by a low calcium, or both.

RICKETS COMPLICATED BY TETANY[10]

In this group of sixteen cases, physical and roentgenologic evidence of rickets was shown in all of them. Six, or 37.5 per cent., were of the severe type, and ten, or 62.5 per cent., were of the moderate type, the diagnosis being based upon the clinical and roentgenologic findings. Four of the severe cases showed definite evidence of healing in the roentgenograms, which was evidently in progress when tetany was superimposed, as, at the time of the blood examination, the calcium averaged 6.3 and the phosphorus 4, with an average product of 25, which is below the value necessary for calcification of bones. Two patients (Cases 3 and 11), aged 11 and 6 months, were still in the florid stage, the product of the calcium and phosphorus being 19.4 and 11.5, respectively. Of ten patients having moderate rickets, eight received breast milk for at least two and one half months, and two were artificially fed from birth. In these ten cases, the phosphorus ranged between 3.3 and 5.6, with an average of 4.4; the calcium between 5.4 and 9.6, with an average of 7.0; while the average product was 31.8. Four cases had a product over 40, and six less than 30. Three of the patients (Cases 9, 11 and 15), aged 5, 6 and 4 months, respectively, were exclusively breast fed. The calcium content in all was below 6. In two patients (Cases 9 and 15), with moderate rickets, the phosphorus was 4.5 and 5.6; in the third (Case 11), with severe rickets, 2.3. The latter breast fed patient, therefore, presented the typical low phosphorus content of severe rickets and the low calcium of tetany.

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[10] Ten white and six colored infants were studied. Their ages ranged from 4 months to 1 year, with the exception of two, aged 24 and 36 months. Tetany developed in all of them during the months January to May, inclusive.

TABLE 3.—*Rickets and Tetany*

Case	Sex*	Age, Months	Weight Lbs.	Weight Oz.	Race	Diet	P, Mg. per Hundred C.c.	Ca, Mg. per Hundred C.c.	Remarks
1. J. McC.	♂	7	14	10	W	Breast fed 2½ months; milk mixture 4 months	5.3	8.3	Convulsions for 1 week; COC, 4.5; Chvostek, —; craniotabes; moderate rickets
2. M. A.	♀	4½	8	..	W	Milk mixture	4.3	5.4	Premature; COC, 3.0; moderate rickets; latent tetany
3. A. McC.	♂	11	16	8	C	Breast fed 3½ months	4.2	4.64	COC, 2.0; severe rickets; active tetany; convulsions 1 week; laryngeal stridor
		12	..	..	..	....	2.77	9.72	After 3 to 5 weeks on cod liver oil and calcium
4. J. M.	♀	5	12	..	W	Breast fed 3 months	5.4	7.72	One of twins; moderate rickets; severe tetany; convulsions 2 days; bronchopneumonia; secondary anemia
5. A. F.	♂	36	..	..	W	Breast fed 19 months	4.2	5.09	COC, 2.0; active tetany; moderate rickets; convulsions 2 weeks; laryngeal stridor
6. P. W.	♂	8	27	..	W	Breast fed 5 months, then breast and milk mixture	4.48	6.36	COC, 2.55; spinal fluid increased pressure; moderate rickets; active tetany; convulsions 4 weeks
							4.88	8.27	After 16 days cod liver oil and calcium
7. N. J.	♀	24	..	..	C	Milk mixture	4.89	6.18	COC, 3.0; severe rickets; active tetany; convulsions, 6 weeks
							4.99	7.65	Cod liver oil and calcium 3 weeks
8. E. B.	♀	7	16	..	W	Milk mixture	4.25	5.55	COC, 1.6; moderate rickets; active tetany; convulsions, 4 weeks; carpopedal spasm; secondary anemia
9. D. G.	♀	5	11	8	C	Breast	4.53	5.82	COC, 1.5; severe rickets; active tetany; convulsions 3 weeks; laryngeal stridor
		5½	..	..	..	....	3.57	11.95	2 weeks, calcium lactate, 15 grains, cod liver oil, 1 dram, 3 times a day
10. M. W.	♀	11	14	..	W	Breast and milk mixture 3 months, then milk mixture	4.73	6.63	COC, 2.0; tetany; moderate rickets; convulsions 1 week
		12	..	..	..	....	3.97	9.41	COC, 10+; cod liver oil, 1 tsp., twice a day; calcium lactate, 15 grains, 3 times a day; calcium lactate and cod liver oil stopped because of diarrhea 2 weeks before blood was taken
11. P. E.	♂	6	13	..	Gipsy	Breast fed	2.31	5.00	Severe rickets; laryngeal stridor; Chvostek; COC, 3.5
12. D. B.	♀	7	12	5	C	Breast 3 mos.; milk mixture 4 months	3.40	8.10	Active tetany; convulsions for 10 days; COC, 3.0; laryngeal stridor; Chvostek; moderate rickets
13. G. M.	♀	11	18	..	C	Breast fed 3 months	5.60	8.00	Convulsions 3 months; laryngeal stridor; Chvostek ++; COC, 3.5; moderate rickets
14. R. J.	♂	9	15	..	W	Milk mixture	3.34	6.55	Moderate rickets; latent tetany; COC, 4.0
15. A. S.	♂	4	13	..	W	Breast fed	5.60	6.10	COC, 3.0; severe tetany; moderate rickets; convulsions 1 week; never sick before
16. C. N.	♂	11	..	..	C	Breast fed 6 months, then milk mixture	3.33	6.86	Severe rickets; active tetany; COC, 2.5; convulsions 2 days
		11½	..	..	..	Milk mixture	3.34	10.19	Phos. cod liver oil, 1 tsp., 3 times a day; calcium lactate, 30 grains, 3 times a day; COC, 10+
		12	..	..	..	Milk mixture	3.99	11.76	

* In this column, ♀ indicates female; ♂, male.

In five cases treated with cod liver oil, 1 teaspoonful, twice daily, and calcium lactate or chlorid 15 grains (1 gm.), three times daily, for periods covering from two to five weeks, a decided calcium increase was noted, approaching the normal level. In two of the cases, the phosphorus showed a decided decrease, and the remaining three were practically stationary. The two cases showing the marked drop in phosphorus under treatment were of the severe type of rickets. In the first of these, the drop in phosphorus was from 4.2 to 2.7, with a rise in calcium from 4.6 to 9.7; and in the second, the phosphorus decreased from 4.5 to 3.5, and the calcium rose from 5.8 to 11.9.

To summarize, tetany may complicate both moderate and severe cases of rickets.

In every case, the blood calcium was below the normal average. The phosphorus was below normal, but higher than in similar grades of uncomplicated rickets.

The average product of calcium and phosphorus was lower in cases of tetany than in uncomplicated moderate rickets, but slightly higher than in severe rickets.

Although in the majority of our cases there was evidence of healing indicated in the roentgenograms, even in those showing the more severe forms of rickets, the product of calcium and phosphorus was in ten cases below the healing zone.

Although there is a relatively high concentration of phosphorus in cases of severe rickets complicated by tetany, the blood picture tends to revert to the relatively low phosphorus and high calcium content in the early stages of treatment.

The clinical symptoms of tetany improve as the calcium content of the blood increases under treatment and the electrical reactions may be normal even before the calcium returns to the normal figure.

CONCLUSIONS

1. In moderate rickets, the phosphorus or calcium, or both, may be moderately lowered.

2. In severe rickets, the phosphorus is markedly reduced, even in those exclusively breast fed, while the calcium may or may not be lowered.

3. In approximately 40 per cent. of our cases of tetany, severe rickets was present. In rickets complicated by tetany, the calcium is considerably reduced. The phosphorus may or may not be reduced. Under treatment, in the severe cases of rickets complicated by tetany, the phosphorus content at first shows a tendency to decrease or to remain stationary.

4. Our studies have demonstrated that there is a more or less definite blood picture in rickets and in rickets associated with tetany, but we feel that these represent two phases of the same disorder rather than two distinct types, and that the blood picture may be affected by extraneous factors and may vary according to the activity or healing of the process.

A SHADOWGRAPH METHOD OF RECORDING OUTLINES OF HANDS *

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The method here described was devised to make a permanent record of the shape and size of the hands of children. The purpose was to obtain (1) a record on which proportions could be measured for the study of pathologic cases; (2) records for future reference and comparison, and (3) a picture that could be utilized for teaching purposes.

We have found that suitable shadowgraphs can be easily obtained in the following way: The hand is firmly placed with palms down over a sheet of sensitized printing paper (Eastman's "velox"). A 110 volt, 100 watt Edison mazda incandescent lamp is then placed 48 inches directly above the middle axis of the hand, and the sensitized paper is exposed for a period of ten seconds. This procedure should be carried on in a dimly lighted room. The print is then developed with the usual developing and fixing reagents.

The method will be found simple, speedy and inexpensive when compared with drawings, photographs or roentgenograms. As to accuracy, it has been determined that the reproduced image coincides to within 1.5 per cent. of the actual measurements of the hand.

One important precaution should be pointed out in order that an accurate reproduction be obtained: In the cases of infants and very young children, owing to the lack of cooperation, there is a tendency to obtain varying degrees of foreshortening, owing to the fact that the hand and fingers are not in close apposition with the sensitized paper. This can be avoided if sufficient care and patience is observed and if the exposure is made at the opportune time.

The accompanying shadowgraphs illustrate the type of cases on which records of this character are of value for study and for purposes of comparison.

Such records have been obtained in cases of endocrine disturbances, including cretinism and pituitary disease, Mongolian idiocy, pulmonary osteo-arthropathies and Still's disease.

Although the number of cases is not large, the accurate measurements possible enable one to point out and confirm previously existing but indefinite opinions that the relative proportions of the hand of the cretin and the Mongolian idiot show characteristic differences. This may be seen in Figures 2 and 3, which show that although the length of the hands are approximately the same, the length of the palm of

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* From The Childrens Medical Service, Massachusetts General Hospital.

the cretin is less than that of the Mongolian idiot, while the length of the fingers of the former is definitely greater than that of the latter.

These shadowgraphs have proved to be satisfactory as permanent clinical records. They are now being used routinely in the children's

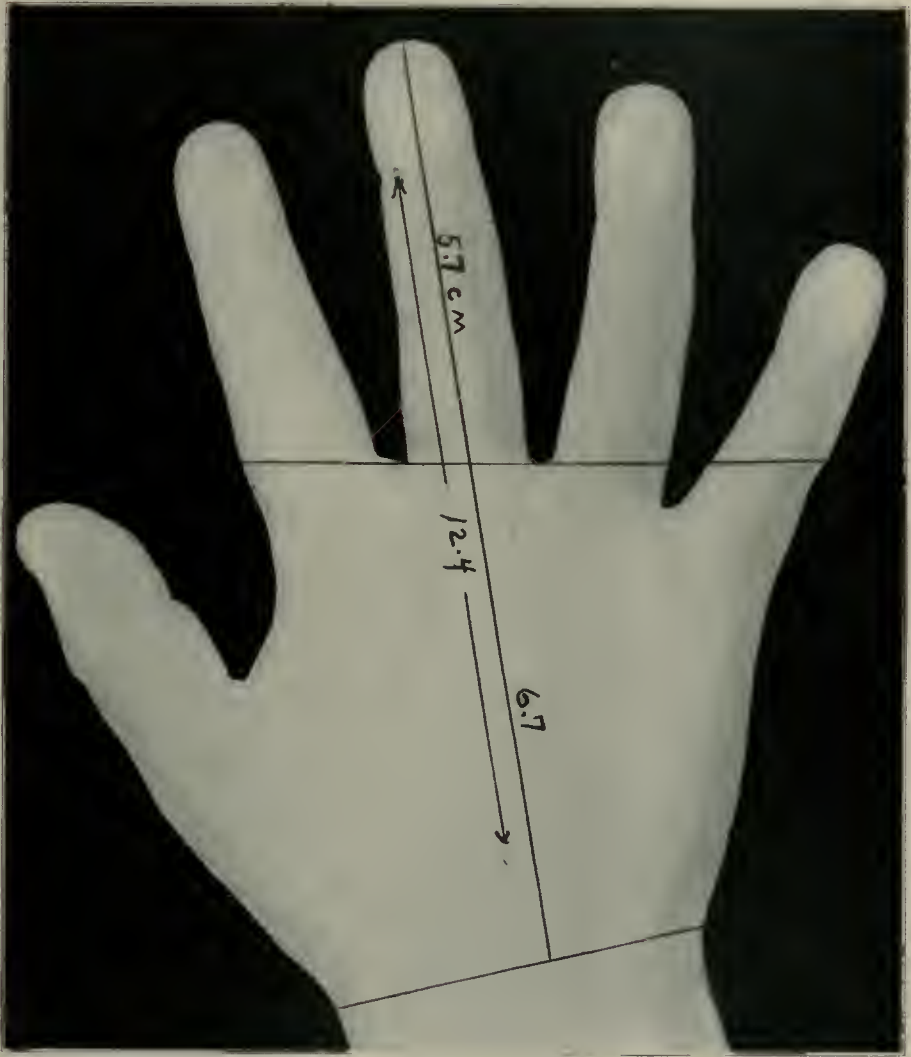

Fig. 1.—Hand of a normal male child, aged 6 years (compare with hand of cretin and Mongol).

medical laboratory of the Massachusetts General Hospital in cases in which a record of growth is desired, and an effect of therapy on abnormalities of shape and proportions might be expected.

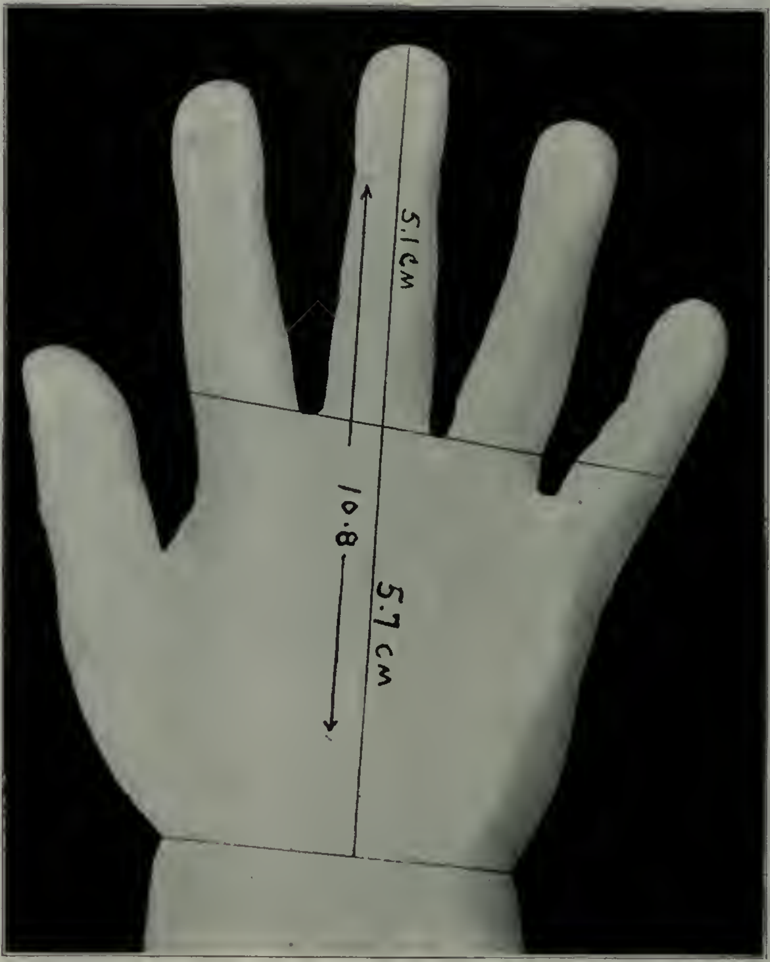

Fig. 2.—Hand of a cretin, a girl, aged 5¾ years. Changes brought in the tissues and skeleton by medication may be compared from time to time.

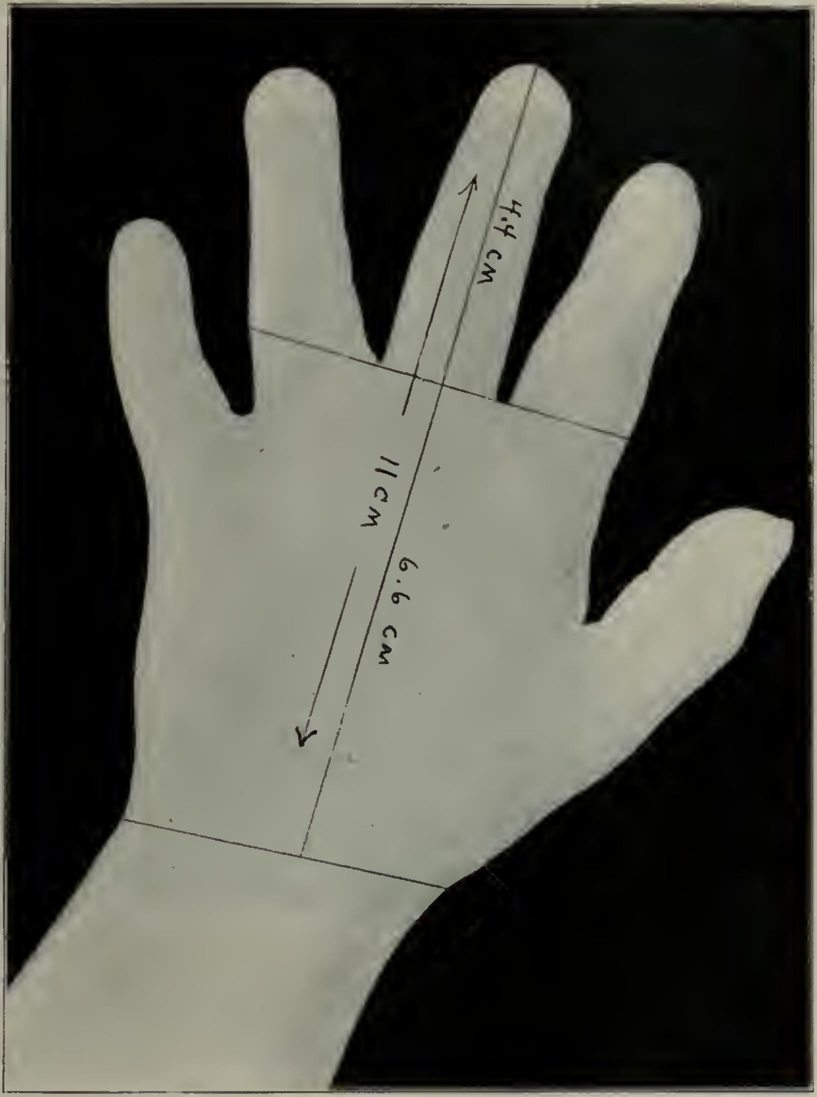

Fig. 3.—The "trident hand" of Mongolian idiocy, that of a girl, aged 6 years. The relative difference between the length of the fingers in this case as compared with those of the normal child and of the cretin should be noted. The hooked little finger is characteristic.

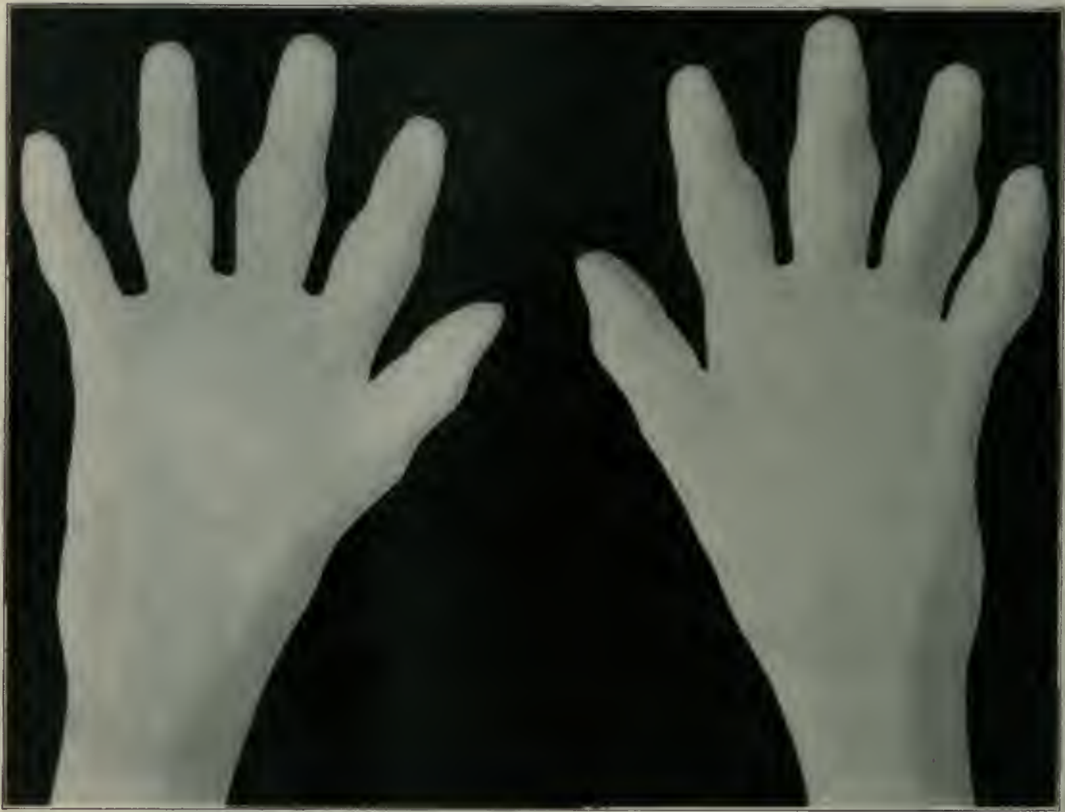

Fig. 4.—Hand of a boy, aged 5 years, showing the characteristic spindleshaped swelling of the fingers in arthritis deformans (Still's disease).

RICKETS IN RELATION TO THE INORGANIC PHOSPHATE AND CALCIUM IN MATERNAL AND FETAL BLOOD *

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Whatever may be the conceptions regarding the pathogenesis of rickets, they all concern themselves to some extent with the metabolism of phosphorus and. calcium. In infantile rickets, the inorganic phosphorus of the blood is almost regularly diminished; whereas, in tetany —a disorder intimately associated with rickets—the calcium content is diminished. It is becoming increasingly evident that rickets occurs earlier in infancy than was formerly believed: that it is a disorder frequently present in the first half of the first year of life. In Schmorl's statistics, which are based on necropsy findings, 97 per cent. of the infants between the ages of 4 and 6 months showed histologic evidence of rickets. When the matter was viewed in this light, and the possibility that prenatal disturbances of metabolism may play a rôle in the etiology was considered, it seemed worth while to ascertain the calcium and phosphorus content of the blood of the pregnant mother and of her infant at birth, and, furthermore, to follow the welfare of these infants and observe whether there is an association between a diminution of these constituents at birth and the occurrence of rickets during the first year of life. As a preliminary, the blood of a number of pregnant women was tested from the fourth month of pregnancy to term. Table 1 gives the results of these examinations. It will be noted that the average percentage of calcium was 10.4 mg., and that of inorganic phosphorus, 2.77 mg. per hundred cubic centimeters; in other words, that both figures fell well within the normal. Similar results have been reported by other investigators. Lamers[1] found 11.6 mg. per hundred cubic centimeters of calcium in pregnant women, as compared with 10.8 mg. in the nonpregnant. De Wesselow[2] found the calcium somewhat diminished at the eighth and ninth month of pregnancy—9.4 mg.—and the inorganic phosphate normal, 2.72 mg. In tests of cows, Meigs[3] and his associates report the calcium to be unaffected by pregnancy or by lactation.

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* Received for publication, July 18, 1923.

* Read in abstract before the Society of Experimental Biology and Medicine (Proceedings **20**:75, 1922).

[1] Lamers, A. J. M.: Ztschr. f. d. ges. Gynäk. u. Geburtsh. **71**:393, 1921.

[2] De Wesselow, O. L. D.: Lancet **2**:227 (July 29) 1922.

[3] Meigs, E. B.; Blatherwick, N. R., and Cary, C. A.: J. Biol. Chem. **37**:1 (Jan.) 1919.

We next collected blood from the umbilical cord at the time of labor and compared it with the blood of the mother obtained shortly thereafter. For the tests of inorganic phosphate, whole blood was used, diluted with approximately six volumes of water, and without the addition of oxalate or some other anticoagulant. Almost immediately after laking the blood, it was tested by means of the Bell and Doisy method. For calcium serum was estimated by means of Lyman's method. The mother's blood was generally secured within twenty-four hours of labor. Trial tests showed no distinction between the blood of women just previous to labor and that obtained twenty-four or forty-eight hours subsequent to parturition. Table 2 summarizes the results of these comparative tests of inorganic phosphate and calcium of the blood. The outstanding feature is the disparity in inorganic phosphate between mother and infant. The average of the mothers' blood was 2.89 mg., and that of the infants, 3.71 mg. per hundred cubic centimeters. The significance of these figures lies in the fact that, in all but one instance, the inorganic phosphate of the infant's blood was higher than that of its mother. The calcium estimations require little comment. The average for the infants was somewhat higher than that for the mothers. The figure 9.75 mg. per hundred cubic centimeters for mother's blood is slightly below the normal for adults. There are few estimations of calcium in the serum of the newborn with which to compare our data. Howland and Marriott[4] tested blood from the umbilical cord in three cases, and found an average of about 10.8 mg. Jones and Nye[5] examined the blood of five babies less than 14 hours old, and reported the calcium content as 12.6 mg. per hundred cubic centimeters.

TABLE 1.—*Phosphorus and Calcium in Blood of Pregnant Women*

				Blood		
Case	Parity	Race	Months Pregnant	P, Mg. per Hundred C.c.	Ca, Mg. per Hundred C.c.	Comment
1	7	White	7½	2.64	10.5	
2	2	White	7	2.50	9.5	
3	1	Negro	8	....	11.4	17 years old
4	4	Negro	5½	3.30	12.0	
5	3	White	8	2.64	9.5	
6	2	Negro	8	2.57	10.7	
7	5	White	7½	3.40	10.5	Wassermann reaction +
8	3	Negro	5½	2.72	9.5	
9	3	Negro	8½	2.37	....	
10	7	Negro	4	2.90	....	
11	3	White	7	2.58	10.1	Case 13, Table 2
12	2	Negro	7	2.72	10.4	
13	4	White	6	2.90	10.3	
Average....................................				2.77	10.4	

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[4] Howland, John, and Marriott, W. McKay: Tr. Am. Pediat. Soc. **28**:202, 1916.

[5] Jones, M. R., and Nye, L. L.: J. Biol. Chem. **47**:321 (July) 1921.

The inequality of the inorganic phosphorus in the blood of mother and new-born infant requires further comment when one considers the solubility and diffusibility of this salt. The difference in the number of red corpuscles in the blood of the adult and the infant does not furnish an adequate explanation. Zucker and Gutman[6] have shown that the inorganic phosphate is distributed equally between red corpuscles and plasma. Tests which we carried out to elucidate this point further led to the same conclusion: the inorganic phosphate of plasma and of whole blood obtained from the cord did not differ from each other more than 0.2 per cent. As is well known, delay in examination of blood plays an important rôle in estimations for inorganic phosphate, leading to a conversion of organic into inorganic phosphorus. Special precaution, therefore, was exercised to carry out the tests as soon as possible after the blood had been shed. In most instances, the interval was not more than from ten to fifteen minutes. It is true that "standing" generally raises the percentage of inorganic phosphate. However, experiments carried out in this laboratory by E. A. Tolstoi showed that the effect of the time factor is variable. Standing for a period of three hours brought about, in some instances, no increase in inorganic

TABLE 2.—*Phosphorus and Calcium in Blood of New-Born Infants and Their Mothers*

Case	Sex*	Parity	Race	Mother's Blood		Cord Blood		Infant's Wt.	Natal Age, Mos.	Duration of Labor Hrs.	Development of Rickets Later
				P, Mg. %	Ca, Mg. %	P, Mg. %	Ca, Mg. %				
1	♂	3	Negro	3.10	11.0	4.28	11.9	7.3	9	24	Marked
2	♂	3	White	2.72	10.1	4.09	10.2	7.4	9	14½	
3	♀	1	Negro	2.64	9.4	4.09	10.1	6.5	9	17½	Moderate
4	♂	3	Negro	3.35	9.5	3.15†	....	7.1	9	36	None
5	♀	1	White	3.46	9.2	4.50	11.2	5.14	8½	13¼	Slight; nursed 6 months
6	♀	6	Negro	3.00	10.7	3.33	....	8.14	10	6	Moderate; 2 carpal centers at birth
7	♂	2	White	2.81	10.3	3.05	9.2	6.9	9	19¼	
8	♀	3	White	2.70	10.0	3.91	11.4	7.6	9	2	
9	♀	3	White	2.72	9.1	3.75	10.2	7.9	9	3½	Slight
10	♀	3	Negro	3.21	10.0	3.75	11.5	5.2	8	13	Moderate; convulsions
11	♂	3	White	2.57	9.3	4.27	10.6	7.7	9	5¼	
12	♀	3	Negro	2.72	10.3	3.21	12.6	4.13	8	11	
13	♂	3	White	3.15	9.6	4.41	10.6	6.8	10	12½	Slight; Case 12, Table 1
14	♂	4	White	2.81	9.4	3.91	11.4	8.0	9	41	
15	♀	4	White	2.63	9.7	2.90	....	7.0	9	4½	Slight
16	♂	3	White	3.10	9.1	3.33	10.8	8.0	9	..	None
17	♀	4	Negro	2.81	10.0	2.90	9.5	7.11	10	1	Marked; nursed 7 mos.
18	..	2	White	2.50	10.2	3.52	11.0	8.5	9	3½	None
19	♀	2	Negro	2.88	9.4	4.17‡	11.1	...	7	6½	Wassermann ++++; baby died same day
20	♂	5	White	2.76	9.5	4.18	10.9	8.13	9	8½	Slight
21	♀	3	White	3.10	9.7	3.27	9.1	7.8	9	3¼	Toxemia of pregnancy
Average				2.89	9.75	3.71	10.75				

* In this column, ♀ represents female; ♂, male.
† Only instance in which mother's blood contained more phosphorus than that of infant.
‡ Premature infant.

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[6] Zucker, T. F., and Gutman, M.: Proc. Soc. Exper. Biol. & Med. **20**:133, 1923.

phosphate. Eight hours standing in the refrigerator resulted in an increase from 2.92 to 3.7 mg., and in another from 3.1 to 3.7 mg.

It should be borne in mind, in considering the inequality of inorganic phosphate in the blood of mother and child, that the excretion of phosphorus in the fetus is very slight. Heubner[7] showed that the amniotic fluid, as well as the urine voided by the infant during the first eight hours of life, contains only traces of phosphorus. This indicates the marked difference in the metabolism of inorganic phosphorus between fetal and postnatal life; for, as is well known, during the latter period the loss of this constituent by way of the urine is great. We should also remember that the distribution of blood phosphorus between mother and infant is disturbed in other fractions. Slemons[8] has shown that the fetal blood is comparatively poor in lipoid phosphorus, owing to the impermeability of the placenta for lipoids. It is possible that this diminution is associated with the comparative increase in inorganic phosphate which we have found.

Although the blood of the fetus is definitely richer in inorganic phosphate than is that of the mother, it is poorer in this constituent than that of infants a few months of age. As stated, fetal blood contained an average of 3.71 mg. per hundred cubic centimeters; whereas, the blood of the normal infant contains about 4.5 mg. Since it has been shown that the inorganic phosphate of the blood tends to fall during the winter and spring, and to rise during the summer months, it may be added that these tests were carried out during June and July. In our experience, infants whose blood contains less than about 3.75 mg. per hundred cubic centimeters of inorganic phosphorus generally manifest other evidences of rickets. These new-born infants, although having an inorganic phosphate content within the rachitic zone, showed no clinical evidences of rickets. In many of the cases, roentgenograms of the epiphyses were taken within the first ten days of life, but in no instance were signs of rickets seen. In one case, in which the inorganic phosphate was but 3.33 mg., two carpal centers were present at birth.

Extraneous factors did not seem to be responsible for the percentage of phosphate. It could not be brought into relation with the duration of labor, or the employment of forceps, with the administration of anesthetics or with the vigor of mother or child. Prematurity does not seem to tend to a diminution, if one may judge from the case of a baby born at six and one-half months, whose cord blood contained 4.17 mg. of inorganic phosphate (Table 2) ; nor does congenital syphilis enter into the question, for in only one instance was the Wassermann reaction positive. Moreover, it has been our experience that the inorganic phosphate in the blood of syphilitic infants is approximately normal. In fact, this test has been of value in differentiating congenital syphilis from rickets in instances in which the roentgenograms were difficult to interpret.

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[7] Heubner, W.: Arch. f. exper. Path. u. Pharmakol. **62**:253, 1910.

[8] Slemons, J. M.: Bull. Johns Hopkins Hosp. **34**:7 (Jan.) 1923.

With these cases as criteria, it was decided to observe whether a relationship would be manifested between the percentage of inorganic phosphate in the blood of the new-born and the subsequent development of rickets during the first year of life. With this object in view, some of the infants were kept under supervision throughout the winter. They were examined and roentgenograms were made in the early spring, when rickets is most prevalent. The results of the roentgenographic examinations of the epiphyses are included in Table 2. With these cases as a basis of comparison, it will be noted that, in four instances, rickets developed in babies which had a particularly high phosphate content at birth: 4.28 mg., 4.09 mg., 4.50 mg. and 4.18 mg. On the other hand, cases with a percentage of 3.15 mg., 3.33 mg. and 3.52 mg. gave no roentgenographic evidence of rickets at the age of about 9 months. It is clear that whatever may be the rôle of prenatal factors in rickets, the percentage of inorganic phosphate at the time of birth is not the determining factor; nor does it indicate whether rickets will subsequently develop. In several cases at the age of 3 or 4 weeks, the inorganic phosphate was found as high as 4.2 mg. or 4.5 mg. per hundred cubic centimeters; which seems to indicate that the percentage is rapidly increased as the result of ingestion of food and the changes in metabolism in the first weeks of life.

SUMMARY

The inorganic phosphate of the blood of pregnant women is approximately normal. The calcium is somewhat diminished at term.

The inorganic phosphate of the blood of the mother is almost invariably lower than that of her infant at birth. This holds true although to a less extent, for the calcium.

The inorganic phosphate of the new-born is generally lower than that of infants 1 month of age or older. However, even when the percentage was within the rachitic range, rickets was not evident by clinical or roentgenographic examination.

No relationship was found between the percentage of inorganic phosphate in the blood of the new-born and the occurrence of rickets during the first year of life.

BOOK REVIEW

ANNALS OF ROENTGENOLOGY. III. DIGESTIVE DISTURBANCES IN INFANTS AND CHILDREN, ROENTGENOGRAPHICALLY CONSIDERED. By Charles Gilmore Kerley, M.D., and Leon Theodore Le Wald, M.D., New York, Paul B. Hoeber, 1923.

This book concerns an interesting series of cases, well illustrated with roentgenograms and briefly discussed. It is questionable, however, whether the work will be of great value to the pediatrician or to the roentgenologist. One can hardly agree with the authors that ".... the subject is covered fairly completely in the series of cases reported...." The technic of roentgen-ray examination, preparation and the like is well described. There is, however, much irrelevant matter and too much detailed treatment for a book with this title. Also, too much emphasis is placed on so-called "gastroptosis." When the habitus of the individual is taken into consideration, actual ptosis or falling down or sinking down of the stomach (or colon) is rarely found. The roentgen ray is of little value in the diagnosis of chronic appendicitis.

CORRECTION

Dr. Cornelia de Lange has called attention to an error in her article appearing in the July issue of the American Journal of Diseases of Children. On page 84, second paragraph, fourth line, the phrase "a liquid in the brain" should read "aliquid in cerebro."

American Journal of Diseases of Children

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STUDY OF ACUTE SECONDARY ANEMIAS IN INFANCY *

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New facts concerning blood destruction and blood regeneration are constantly necessitating a revision of our conceptions of these conditions. Certain results are based upon generally accepted observations so that one is fairly safe in making definite deductions from them. Blood destruction is one of the routine tasks of the body and the replacement is the result of the continuous activity of a widely distributed hematopoietic system. Under normal conditions, the blood tissue is so constituted that it can withstand sudden and considerable changes, and the cells of the blood tissue are so flexible that throughout these changes their normal shape is retained. The rate of regeneration normally depends on the rate of destruction, which has been variously estimated at one tenth, one fifteenth or one thirtieth of the total blood each day.

On the other hand, in cases of secondary anemia in which transfusions with a blood of a compatible group have been carefully studied, these cells have been known to remain in the circulation from forty to fifty days; and in healthy subjects they have been known to remain as long as 100 days. These same studies have brought out another interesting point: In the elimination of these cells there is a definite periodicity showing that different cells have definite life cycles. Under normal conditions of exercise, the rate of regeneration and destruction may be changed. If the animal is unaccustomed to exercise, there will be an increase in the rate of destruction until he becomes adjusted to his increased activities. Undoubtedly, there is a very delicately balanced coordination between these two processes.

The methods of normal blood destruction are phagocytosis and fragmentation, and under abnormal conditions destruction may be brought about by the added factor of hemolysis. Under normal con-

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* Received for publication, June 6, 1923.

* Read at a meeting of the American Pediatric Society.

ditions, hemolysis probably plays little part, but in pathologic conditions, by hemolytic, toxic or serologic changes in the blood or body tissues, either rapid or slow destruction may be produced by this method. The facts relating to phagocytosis have been fairly well established. The large endothelial cells in the spleen take up red blood cells and destroy them; blood pigment is at times present in the Kupffer cells of the liver, and under certain conditions the lymph glands and bone marrow may perform like functions. In man, fragmentation probably plays a more important rôle in normal blood destruction than does phagocytosis. Normal blood contains a small number of fragmentation forms, but under pathologic conditions of severe anemia they often appear in large numbers. These fragmentation forms are portions of old or young cells which become fragmented while circulating, the old cells undergoing fragmentation either because they have passed their time period or because they are brought under unusual stress and are unable to withstand the wear and tear of this emergency. The young cells become fragmented because of their immaturity and consequent inability to stand the functional strain.

The bone marrow normally produces just a sufficient number of red blood cells to replace those destroyed. Any loss or destruction of these cells stimulates the marrow proportionally to the loss or destruction of blood, and this response will continue as long as the bone marrow is functionally capable. When the marrow becomes exhausted, compensation fails and anemia results. So long as the number of circulating cells remain constant, it may be assumed that a balance exists between blood destruction and blood formation, but if the hemoglobin percentage and the blood count are rising or falling, it is difficult, without special methods, to estimate the relative rate or change of blood destruction and regeneration. Some direct knowledge of a quantitative nature concerning the rate of blood formation may result from employment of some of the newer methods of studying the cells by vital staining, and the changing picture from day to day may, by these methods, give us some important estimations of the actual state of the blood-forming organs. For this purpose, the blood must be followed from day to day, and individual cells must be studied and compared in order that their composition may be determined. This has been made possible by the application of vital staining, in addition to the usual methods employed in studying the morphology of the various types of blood cells. By such means, we are able to estimate the effort required of the blood-forming organs in maintaining the normal level. From this point of view, the following signs of regeneration in the red cells are recognized: Nucleated red cells, Cabot's rings, Howell-Jolly bodies, megaloblasts, poikilocytes, polychromasia, reticulation, megalocytes, macrocytes, mitochondria and certain types of stippling. Fragmentation and shadow forms are the generally recognized signs of degeneration in the red cells. There is a wide difference of opinion as to the interpretation of the evidence of degeneration in the red cells.

The classification of several of the abnormalities found in red cells during periods of strain is still in doubt. Opinions vary as to the part played in the life of the cell by microcytes. By some, these cells are considered an evidence of degeneration, because these cells occur in anemias and are the beginning of the process of fragmentation.

We have frequently found them in anemias and have noticed that they have this peculiarity: They appear in blood pictures in which there are marked evidences of accepted regeneration, and we have found them containing reticulum and mitochondria, both fairly well accepted signs of regeneration. These microcytes are usually uniformly colored and many of them show poikilocytosis. These same evidences of regeneration we have found in the macrocytes also, and both types of these oversized and undersized cells contain the embryonic basophilic substance giving rise to the abnormal coloring in the blood known as polychromasia. There is little in the literature regarding the character of anisocytosis, but our own studies have convinced us that anisocytosis is a sign of regeneration. Stippling is one of the accepted evidences of regeneration, and we have so considered it; but we have frequently encountered a fine basophilic stippling around the periphery of shadow forms which, of course, are degenerating cells. Mitochondria are likewise, in our opinion, an evidence of regeneration, though there has been much debate as to whether these are artifacts or bacteria or true structural parts of the cells. They occur in young red cells and can be stained with Janus green. They usually occur in about the same number and in the same type of cells as reticulum, which is brought out in the vital staining method by brilliant cresyl blue. The two phenomena represented by mitochondria and reticulum are the most reliable in estimating the amount of regeneration from day to day.

A determination of the number of blood platelets also yields valuable information concerning the activity of the bone marrow. Platelets are definitely diminished when the marrow regeneration is defective. Their decrease below a certain number (approximately 50,000 to the cubic millimeter) indicates that the marrow is nearing a dangerous functional margin.

We know comparatively little about the regeneration or degeneration of the white cells. Much has been written on their morphology, and under certain pathologic conditions the types of cells have been carefully studied, but the exact processes of regeneration of the whole bone marrow and the function of the hemopoietic system is little understood. There are but three accepted indications of youth in the white cells; namely, the number of lobes in the nucleus, two or less indicating youth; the presence of Türck's irritation forms, and the appearance in the blood stream of immature forms, myelocytes and myeloblasts. The white cell, unlike the red cell, dies in the blood stream, and shows the evidence of this death in vacuoles in other than large mononuclear cells, in fragmentation, in poorly staining cytoplasm or in densely staining swollen nuclei. The signs of disintegration are more easily determined in the polymorphonuclear cells than in the lymphocytes, and more often in the large lymphocytes than in the small. We know the lymphocyte is more viable than the cells of the granular series, as this can be easily demonstrated by sealing blood beneath a cover slip, when the granular series and the red blood cells disappear, while the lymphocytes remain without much alteration except vacuoles for a number of days after the others have all disintegrated.

Certain evidences of regeneration in the white cells are capable of demonstration by vital staining. The segregation apparatus of the white cells is a protective response on the part of these cells, which may be brought out by vital staining with brilliant cresyl blue. The number of granules in the segregation apparatus in each type of cell is constant. The exact temperature and strength of dye for demonstrating the segregation apparatus in normal cells has been carefully worked out. Under abnormal conditions, either the segregation apparatus will not stain or there is a difference in the form of the segregation apparatus; that is, the manner in which the dye granules are taken up and arranged. This is a study which we believe will, with more care and observation, be as valuable an indication of the state of the white cell producing organs as reticulum and mitochondria are in the study of the red cells.

All white cells are motile, and in a wet preparation movements of the pseudopodia can be observed. Normally, these movements are slow and coordinated, but when the cell is old or is about to die, they either do not have any movement or the movements are not coordinated. The conditions under which such studies are carried out must be carefully controlled because the slightest change in technic may alter the interpretations. At the present time, we need more intensive studies along these lines. The accompanying tabulations bring together the accepted and suggestive evidences of regeneration and degeneration in the blood cells. We have grouped these so that in our studies of acute anemias we can more accurately determine the functional condition of the bone marrow and whether the trend of the condition is toward an increased destruction or an improved regeneration.

Accepted evidence of regeneration in white cells.

1. Myelocytes, myeloblasts, or Arneth's shift to left.
2. Türck's irritation cells.

Accepted evidence of degeneration in white cells.

1. Fragmentation.
2. Poorly staining cytoplasm.
3. Swollen nuclei.
4. Heavily staining nuclei.
5. Vacuoles other than in endothelial cells.

Suggestive evidence of regeneration in white cells.

1. General increase in size.

Suggestive evidence of degeneration in white cells.

1. Loss of mottled appearance of nucleus with uniform staining.
2. Decrease in number of granules.
3. Nuclear swelling with smoothing of outline and decrease in number of lobes.
4. Failure of pseudopodia to form under proper conditions.
5. Failure of segregation apparatus to function under proper conditions.

Accepted evidence of regeneration in red cells.

1. Nucleated red cells.
2. Reticulation.
3. Polychromasia.
4. Poikilocytosis.
5. Howell-Jolly bodies.
6. Cabot's rings.
7. Megaloblasts.
8. Megalocytes.
9. Macrocytes.
10. Stippling.

Accepted evidence of degeneration in red cells.

1. Ghost or shadow forms.
2. Achromasia.

Abnormalities in red cells yet in question.

1. Fragmentation.
2. Microcytes.
3. Anisocytosis.
4. Mitochondria.

Suggestive evidence of degeneration in red cells.

1. Stippling in shadow forms.
2. Crenation.

The acute anemias which we have studied in children can be placed in four groups according to the method of their production: (1) Mechanical loss of blood; (2) hemoglobin deficiency; (3) destruction of bone marrow; (4) bone marrow and blood stream complex.

In the first group, due to mechanical loss of blood, the simplest type is that in which acute hemorrhage occurs, and the predominating picture is that of regeneration. Evidences of regeneration may be noted as early as fifteen minutes after the hemorrhage, in the appearance in the blood stream of normoblasts; and the red cells show reticulum and mitochondria, with anisocytosis and polychromasia and an immediate increase in the white cells. An illustration of this type of hemorrhage was that found in a 12-year-old girl who entered the hospital a few hours after an acute hemorrhage from a hemangioma of the jaw which had been treated by radium. The clinical picture was typical; the hemoglobin was 20 per cent.; the red cells numbered 1,800,000, the white cells, 22,000, with a differential count of polymorphonuclears, 70 per cent; small lymphocytes, 15 per cent.; large lymphocytes, 12 per cent.; eosinophils, 3 per cent.; basophils, 2 per cent. The signs of regeneration were quite marked in the red cells. There were 2 per cent. of normoblasts, 6 per cent. of reticulum, 5 per cent. of mitochondria; and there were fairly well marked polychromasia and slight anisocytosis and poikilocytosis. An occasional Cabot's ring and numerous Howell-Jolly bodies were found, and there was a very slight achromasia. The general size of the white cells was increased and a large percentage of the polymorphonuclear cells had two or less lobes; that is, there was a definite shifting of Arneth's formula to the left. An occasional broken down polymorphonuclear cell was noted. At the end of ten days, the red cells had returned almost to normal; there were no normoblasts, and the mitochondria and reticulum had returned to normal, though there were signs of achromasia, polychromasia and anisocytosis. One month later, the blood picture was normal.

Whipple has demonstrated that the return to normal in anemia caused by hemorrhage is very rapid, provided the hemorrhages are not repeated too often and the amount of blood lost is not much more than 50 per cent. of the total blood volume. In such hemorrhages, there is a marked stimulation of the bone marrow, and if proper dietary factors are supplied, regeneration will be very rapid. However, when the hemorrhages are repeated at short intervals and the dietary factors that stimulate bone marrow production are poor or lacking, the return to the normal level will be very slow. By repeated bleeding and by keeping the experimental animals on a diet inadequate in factors that stimulate bone marrow production, the functional level of the bone marrow may be reduced and an anemia produced which it is very difficult to overcome.

This type of anemia we have met in a number of cases of hemorrhages recurring at short intervals. The blood in such cases, if studied over a long period, will show little or no change. The hemoglobin is diminished and the number of red cells reduced. There is usually a moderate amount of achromasia, but little or no sign of regeneration. If the anemia has not been "set" by having continued for a long period, the bone marrow stimulation may be brought about by dietary and hygienic measures. When the anemia has become "set," more radical stimulation, such as transfusion, is necessary to raise again the functional level of the bone marrow.

The second group in which the anemia is caused by deficiency in hemoglobin is large. This type of anemia is found most commonly in premature infants, in twins and in infants born of anemic mothers or of mothers who have had some acute infection during the last few months of pregnancy. In all these infants there is a definite lack of iron deposited during fetal life. This type of anemia is also found in infants who have had a diet definitely inadequate in iron over a long period. It is well known that, even in normal infants, the deposit of iron in the liver is probably only adequate for the first six or eight months. After this age, whether the child is on breast milk or on cow's milk, the supply of iron is not sufficient for the needs of the infant. Fortunately, at about this period, most infants receive other foods which contain considerable quantities of iron. This type of anemia is often spoken of as alimentary anemia, and we have met it most often in infants between 10 and 18 months of age. This is probably the same type of anemia as is met in rickets; at least, the blood picture in rickets we found so nearly similar that we have placed the anemia of rickets in this second group, although the study of iron metabolism in rickets does not show any deficiency in iron.

The blood picture in this type of anemia shows a marked reduction in hemoglobin, out of proportion to the reduction of the red cells. The evidences of regeneration are slight, and there is little or no evidence that degenerative processes are going on. The red cell count was rarely less than 2,000,000, averaging between 2,500,000 and 3,500,000, with a hemoglobin that ranged between 20 and 40 per cent. Normoblasts are only occasionally found. There is usually marked poikilocytosis and achromasia, and the microcytes are increased. The number of macrocytes and the polychromasia are not a striking part of the picture.

Reticulum and mitochondria occur in from 2 to 4 per cent. of the cells. As signs of degeneration in the red cells, fragmentation is usually not marked.

The white blood series show essentially a normal picture. The number of cells may be slightly increased, rarely reaching 15,000 unless complicated by an infection. The ratio of granular cells to nongranular cells remains normal unless there are complications. Signs of regeneration in the white cells are shown by a tendency toward the appearance of myelocytes and large, young looking mononuclears, which may at times be quite a striking part of the picture. Degeneration in the white series is occasionally shown by the presence of fragmenting or fragmented cells of the granular series.

The anemia in this second group is one of the most persistent and often it is difficult to alter the blood picture. By proper dietary measures and by the administration of iron, the simpler cases may often be affected; but even in these simple cases, the number of cells will increase more rapidly than their hemoglobin content. There is considerable experimental data to show that a negative iron balance exists in some form, and this is one of the types of secondary anemia which is often "set," as Whipple expresses it. In the more acute cases, those in which the hemoglobin is below 30 per cent., we have obtained the best results from repeated small transfusions, and we have found that this group requires a larger number of transfusions before very marked signs of bone marrow regeneration are evident. In fact, we have often given as many as eight or ten small transfusions at three or four day intervals before any signs of bone marrow regeneration appear.

One of the most interesting clinical observations in connection with this transfusion is that the appetite, which is usually very poor, has been markedly stimulated and the general well-being of the child definitely improved. Of course, the improved appetite assists in the dietary therapeutics, but even with this aid, the blood picture returns very slowly to normal. Bone marrow punctures in these cases substantiate the general blood picture already described. The bone marrow cells show definite achromasia, but signs of regeneration and degeneration are not especially in evidence. The bone marrow appears to be fairly normal except that it is regenerating more slowly; but there is not much evidence of abnormality in the character or the number of the bone marrow cells.

The third group, which we have termed the anemias with destruction of bone marrow, is the most difficult of interpretation. The study of the blood picture and the bone marrow in these cases shows that the processes of destruction are going on more rapidly than those of regeneration. At the extreme end we have a picture of almost complete aplasia of the bone marrow, and the different gradations, from the extreme to conditions in which it is difficult to say which process is in the ascendency, are a challenge to one's powers of discrimination. The characteristic blood picture of this group is a hemoglobin percentage often below 20 and rarely above 30, and a relatively low red count. Shadow forms and fragmentation of the red cells may be quite marked, but there is little poikilocytosis and only a slight tendency to anisocytosis or polychromasia. The percentage of reticulum and mitochondria is so low that one might say both are absent. One of the most prominent features of this type of anemia is the marked reduction in the number of platelets and in the granular series of the leukocytes.

The platelets are often diminished to below 50,000 per cubic millimeter. In certain cases of bone marrow functional deficiency, however, the platelets may not be markedly affected, and, of course, this in itself is helpful in prognosis. In fact, we are led by our studies to believe that it is of more significance than the leukopenia. Of course, with the reduced platelet count, the tendency to hemorrhage is often one of the most alarming and grave symptoms of this type of anemia. The leukopenia is largely a reduction in the granular cells. The white count is often between 1,000 and 2,000 and is rarely over 5,000. The polymorphonuclear and transitional cells may be as low as 2 per cent. and are usually less than 20 per cent. of the total count. The mononuclear cells present show marked variation in size, often presenting signs of vacuolation and definite staining defects. The granular leukocytes show definite fragmentation and vacuolation and are usually young forms with few lobes to their nuclei. The bone marrow in these cases shows a partial, or in the extreme cases a complete replacement by a yellow fatty gelatinous substance. These extreme cases are termed idiopathic aplastic anemia. However, as far as the blood picture and the bone marrow are concerned, there are a certain number of cases in which the aplasia is not complete and is at least only temporary. In these borderline cases it is often impossible to say which process, degeneration or regeneration, is going to win. We have followed a number of cases of this type of anemia, some of which progress steadily to the fatal termination of a true aplastic anemia. In others, which at certain stages had the identical type of blood picture, patients have recovered. We feel, therefore, that conditions other than the so-called idiopathic can produce an aplasia, and we see no reason why they should not be put in this group until the blood picture changes, as it is often impossible to say whether regeneration will continue to completion. Again, in these cases, we have had the best results from repeated small transfusions. We have followed cases which, at first, clinically, it was hard to differentiate from aplastic anemia and also cases which it was difficult to differentiate from aleukemic leukemia, though I do not mean to infer that these two processes are alike or that there is any confusion in determining which is which. In neither of these conditions do we know the etiologic factors. In our opinion, the toxic results of infections play a most important part in the production of both these types of conditions. Just as a complete or partial aplasia may be experimentally produced by benzene, roentgen ray or radium, so various types of infections may produce the same results.

In the fourth group is presented a complex picture of blood destruction, occurring partly in the blood stream and in part involving the bone marrow. The blood picture in these cases usually shows the definite signs of degeneration and regeneration. The bone marrow picture is one of fairly marked activity as shown by the presence of a high proportion of reticulum, mitochondria, normoblasts, macrocytes, microcytes, poikilocytes and polychromasia. This is also shown by a definite increase in the number of young polymorphonuclears. Signs of toxic effect on the cells in the circulation is shown by the marked achromasia and numbers of shadow forms with fine granules around the periphery. This is the type of stippling which we have mentioned as occurring with degeneration rather than with regeneration. The white cells also show increased vacuolation, swollen nuclei or poorly staining cytoplasm. This likewise indicates the toxic effect on the white cells in the blood stream. The white count in such a condition may be high. The most prominent feature of the blood picture is the increased destruction of the white cells, both young and old.

This is the condition of acute anemia often found in acute pyogenic infections, and the blood picture, if followed carefully, will give a good estimate as to how the process is progressing. During such an infection, we have followed the blood and bone marrow conditions from a stage of marked hyperplasia to one of complete aplasia, a single case presenting the complex picture which this group is capable of exhibiting. In these cases, blood transfusions are of more value than any other type of treatment except when there is a direct blood stream infection or septicemia. The transfusions are of more effect if given at a time when signs of destruction or beginning hypoplasia or defective functioning of the bone marrow are evident. We have not found transfusions of much value during the period of hyperactivity of the bone marrow. In all our cases in which transfusions have been employed, we have given small amounts, from 30 c.c. to 60 c.c. at short intervals. We believe that this is a more valuable method of transfusing than the more usual large transfusion given at longer intervals, and this coincides with the experimental work of Robertson, who showed that, in animals made plethoric by large transfusions, there was a lessened activity of the bone marrow. This is, of course, contrary to the results desired, and, except in the case of great loss of blood, there is little or no need of bringing up the blood volume, as the normal blood volume is kept at a remarkably constant level. Since we have adopted this method of small repeated transfusions our results have been better, especially in cases belonging to the second and third groups.

The accompanying illustrations present the various pictures of anemia, with the processes of regeneration and degeneration clearly defined as studied by the vital staining method.

No studies of acute anemia can be dogmatic as to either absolute diagnosis or modes of treatment, but we feel that our studies help to give us a better understanding of the bone marrow activity and assist in the clearer estimation of the progress of these acute anemias.

We have used two methods of vital staining, supravital (dry) and vital (wet). For both methods, the slides and coverslips are washed in soap, passed through alcohol and dried. The stain, which is made in absolute ethyl alcohol, is spread on the slide or coverslip just as a blood smear is made. The alcohol evaporates quickly, leaving a thin coat of dye on the glass. To complete the supravital technic, a drop of blood is smeared on the slide or cover glass on top of the coat of dye. When dry, the smear is dyed with Wright's stain in the ordinary manner. This makes a permanent preparation. To complete the vital method, a drop of blood is put on the slide on top of the coat of dye, covered with a cover slip and the edge sealed with hot paraffin. When kept at body temperature, the cells slowly take up the dye and can be observed as in the blood stream. We have used Janus green, brilliant cresyl blue and neutral red. Janus green brings out the mitochondria in both red and white cells by the vital method. Brilliant cresyl blue stains the embryonic material in the red cells in both the vital and supravital methods and brings out the segregation apparatus in the vital. Neutral red also stains the segregation apparatus in the vital method. The dilution of dye used is important, for when too strong it will kill the cells by the vital method, and prevents ameboid movement and other normal cell processes. We find that 0.05 per cent. is most satisfactory if but one dilution is to be used. In the supravital methods, as high as 1 per cent. can be used. In the vital method, as low as 0.005 per cent. may be necessary to prevent death of the cells.

(See next page for plate.)

Explanation of Plate

Fig. 1 (Group 2, No. 1).—Blood picture in anemia; before transfusion: hemoglobin, 28 per cent.; red blood count, 3,384; white blood count, 12,200; polymorphonuclears, 36 per cent.; small lymphocytes, 59 per cent.; large lymphocytes, 1 per cent.; transitionals, 4 per cent.; eosinophils, 1 per cent.; *1*, fragmented red cell; *2*, laked red cell; *6*, achromasia; *12*, poikilocytes; *18*, ghost form (stain, Cunningham's vital).

Fig. 2 (Group 2, one plate only).—Blood picture in anemia: marked reaction to one transfusion: *3*, microcyte; *5*, reticulated red cell; *6*, achromasia; 9, megalocyte; *10*, megaloblast; *12*, poikilocytes; *17*, polychromasia (stain, Cunningham's vital).

Fig. 3 (Group 2, No. 2).—Blood picture one month later, after three transfusions; hemoglobin, 41 per cent.; red blood count, 4,400,000; white blood count, 11,200; polymorphonuclears, 26 per cent.; small lymphocytes, 56 per cent.; large lymphocytes, 6 per cent.; transitionals, 10 per cent.; *1*, fragmented red cells; *4*, transfused red cells; *6*, achromasia; *12*, poikilocytes; *19*, stippling in red cells (stain, Cunningham's vital).

Fig. 4 (Group 2, No. 3).—Blood picture one month later, after seven transfusions: hemoglobin, 60 per cent.; red blood count, 5,650,000; white blood count, 11,800; *1*, fragmented red cells; *2*, laked red cell; *3*, microcytes; *4*, transfused red cell; *5*, reticulated red cell; *6*, achromasia (stain, Cunningham's vital).

Fig. 5 (Group 2, No. 4).—Blood picture one month later, after ten transfusions: hemoglobin, 61 per cent.; red blood count, 5,856,000; white blood count, 8,200; polymorphonuclears, 40 per cent.; small lymphocytes, 40 per cent.; large lymphocytes, 20 per cent.; *3*, microcytes; *4*, transfused red cell; *5*, reticulated red cell; *6*, achromasia; *7*, Howell-Jolly body; *8*, nucleated red cell; 9, megalocyte (stain, Cunningham's vital).

Fig. 6 (Group 3, No. 1).—Blood picture before transfusion: hemoglobin, 32 per cent.; red blood count, 1,840,000; white blood count, 2,700; polymorphonuclears, none; small lymphocytes, 6 per cent.; large lymphocytes, 92 per cent.; transitionals, 2 per cent.; *1*, fragmented red cell; *5*, reticulated red cell; *6*, achromasia; *12*, poikilocytes; *15*, large lymphocytes (stain, Cunningham's vital).

Fig. 7 (Group 3, No. 2).—Blood picture two weeks later, after three transfusions: hemoglobin, 43 per cent.; red blood count, 2,000,000; white blood count, 4,200; polymorphonuclears, 32 per cent.; small mononuclears, 24 per cent.; large mononuclears, 44 per cent.; *4*, transfused red cell, *5*, reticulated red cell; *6*, achromasia; *9*, megalocyte; *14*, small lymphocytes; *15*, large lymphocytes; *16*, polymorphonuclears; *19*, stippling red cell (stain, Cunningham's vital).

Fig. 8 (Group 3, No. 3a).—Blood picture two weeks later, after six transfusions: hemoglobin, 68 per cent.; red blood count, 4,100,000; white blood count, 7,600; polymorphonuclears, 23 per cent.; small lymphocytes, 62 per cent.; large lymphocytes, 12 per cent.; transitionals, 3 per cent.; *5*, reticulated red cell; *13*, segregation apparatus; *14*, small lymphocytes; *16*, polymorphonuclears (stain, wet vital BCB).

Fig. 9 (Group 3, No. 3b).—Blood picture one month after entry, after six transfusions: hemoglobin, 68 per cent.; red blood count, 4,100,000; white blood count, 7,600; polymorphonuclears, 23 per cent.; small lymphocytes, 62 per cent.; large lymphocytes, 12 per cent.; transitionals, 3 per cent.; *3*, microcyte; *11*, mitochondria; *14*, small lymphocytes; *15*, large lymphocytes (stain, wet vital Janus green).

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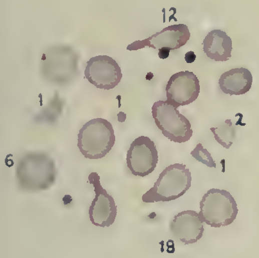


FIG. 1

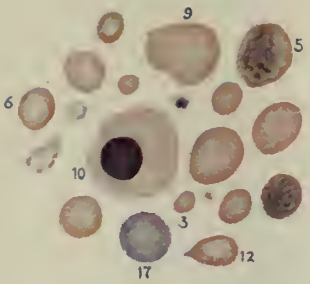


FIG. 2

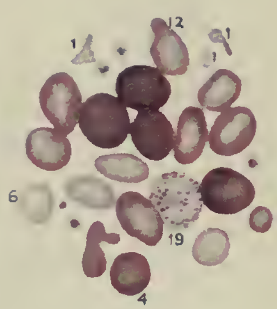
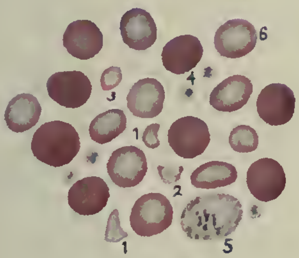


FIG. 3



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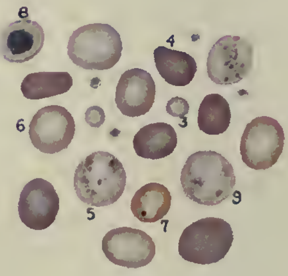

FIG. 5

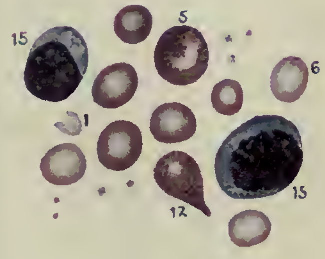

FIG. 6

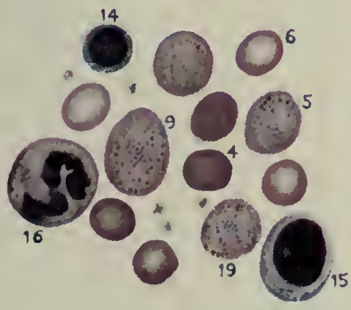

FIG. 7

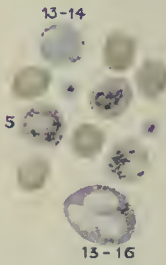

FIG. 8

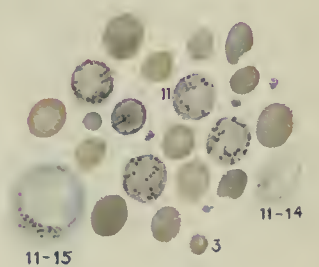

FIG. 9

THE INORGANIC CONSTITUENTS OF HUMAN MILK WITH PARTICULAR REFERENCE TO RACIAL VARIATIONS *

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As far as we know, there have been no analyses of the mineral content of human milk with reference to possible racial variations. Our purpose in this work was to make complete mineral analyses of, or at least to include in our study, those elements which are thought to have an influence on the production of rickets, and then to see whether there is any constant difference in the milk from those races which are prone to have this disease and those which are not so susceptible.

This problem has been attacked from the standpoint of individual elements, but only once as far as we know from the standpoint of a complete mineral analysis. Bahrdt and Edelstein [1] collected data which showed that the calcium content of the milk from mothers whose children were rachitic was much less than that of mothers whose children were nonrachitic. The average content for the former was 22.14 mg. per hundred cubic centimeters of milk, and for the latter, 30.43 mg. Von Meysenbug [2] reported that he found no difference in the inorganic phosphorus content of the milk from these two classes of mothers. Brown, Courtney, Tisdall and MacLachlan [3] reported two complete mineral analyses of human milk, one from a mother nursing a child with tetany, and the other from a mother nursing a child with rickets. In the first instance, they found the calcium slightly reduced, and the total phosphorus and potassium higher than normal. In the second instance, the calcium and phosphorus were decidedly reduced, and the sodium and chlorin increased.

Negroes and Italians are especially susceptible to rickets. Perhaps the Jews as a race have the fewest cases of rickets among their breast-fed infants, although they are by no means free from it. For the sake of simplicity, we divided our cases into only two groups: the white,

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* From the Department of Pediatrics of Western Reserve University, and Lakeside Hospital.

[1] Bahrdt and Edelstein: Jahrb. f. Kinderh. **72**:16 (supplement), 1910.

[2] Von Meysenbug, Ludo: Inorganic Phosphate Content of Breast Milk of Mothers with Normal and with Rachitic Infants, Am. J. Dis. Child. **24**:200 (Sept.) 1922.

[3] Brown, Alan; Courtney, A. M.; Tisdall, F. F., and MacLachlan, I. F.: Arch. Pediat. **39**:559 (Sept.) 1922.

which includes a number of nationalities, and the colored race. We admit in advance that any differences shown in the ash composition of the milk does not necessarily explain the difference in the incidence of rickets. Other constituents of the milk, such as the fat, protein and carbohydrate, and the antirachitic vitamin, may be more important. Also, this takes no account of well established factors, such as environment and the pigment content of the skin.

The samples of milk were obtained in nearly all instances at the infant welfare stations of the Cleveland City Health Department. Only in a few cases was rickets evident clinically. Many of the infants doubtless would have been so afflicted but for the custom of giving all belonging to the colored race cod liver oil after they are from 1 to 2 months old.

No attempt was made to obtain a mixed sample of the various portions of the nursing. The mothers were simply told to fill a 60 c.c. flask. Sisson and Denis [4] found no constant differences in the chlorid content of the various portions. We have, in this laboratory, obtained a considerable number of samples of the fore, middle and after portions and analyzed them for calcium. In no instance was there more than a slight difference, and this when present was not constant for any one part. We have not checked all of the salts in this way, but believe that any error, if present, would be unimportant in consequence of a fairly large number of analyses. The comparison of our results with those of Holt, Courtney and Fales [5] and other investigators who used mixed or twenty-four hour samples shows that our method has been quite satisfactory.

The milk was analyzed for calcium, potassium, sodium, inorganic phosphorus, total phosphorus and chlorids. We did not attempt to determine either magnesium or iron. In reviewing our results, we found that the sodium results showed a marked variation and that there was frequently a lack of constancy in the duplicate analyses. For these reasons, we have decided not to include them in this report.

METHODS

For calcium, sodium, potassium and chlorids, the milk was evaporated in 10 c.c. amounts, and the residue dried and ashed at a low temperature. The ashing instead of being done by the method of Stölte,[6] as advised by most chemists, was carried out in an electric furnace, the walls of which were never hot enough to be even a dull red. This requires a somewhat longer time, often several days, but requires little attention during the process. We have repeatedly heated potassium chlorid in this manner without there being any loss in weight. The ash to be used for calcium, potassium and sodium was dissolved in dilute hydrochloric acid. That used for chlorids was dissolved in 5 per cent. nitric acid. The calcium, potassium and sodium were determined with the methods described by Kramer and Tisdall.[7] Our unsatisfactory results on the sodium we attribute to the small amount of this element present. Ten cubic centimeters of breast milk contains

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[4] Sisson, W. R., and Denis, W.: Studies on Inorganic Constituents of Milk, Am. J. Dis. Child. **21**:389 (April) 1921.

[5] Holt, L. E.; Courtney, A. M., and Fales, H. L.: A Chemical Study of Woman's Milk, Especially Its Inorganic Constituents, Am. J. Dis. Child. **10**:229, 1915.

[6] Stölte: Biochem. Ztschr. **35**:104, 1911.

TABLE 1.—*Complete Results of Analyses*

Serial No.	Age of Mother, Years	Age of Baby, Weeks	Race*	Parity	Date	Ca	K	Inorganic Phos.	Total Phos.	Cl
1	37	7	O	?	11/ 9/21	28.83	62.48	5.7	17.55	45.87
2	18	4	J	1	11/ 9/21	39.93	47.96	4.7	17.95	.....
3	25	32	O	1	11/ 9/21	20.72	54.88	6.1	16.55	.....
4	30	10	It	4	11/ 9/21	36.12	52.23	7.6	14.27	.....
5	21	28	C	1	11/16/21	27.43	40.29	8.0	14.15	48.17
6	17	12	O	1	11/16/21	25.43	43.30	5.1	10.40	60.50
7	..	10	O	1	11/16/21	29.37	52.71	3.7	13.50	51.75
8	23	18	A	2	11/28/21	38.67	60.70	4.9	15.22	81.87
9	28	28	C	1	11/28/21	23.62	50.72	4.3	13.09	40.96
10	23	24	O	2	11/28/21	24.25	81.25	...	13.95	37.32
11	23	10	J	2	11/28/21	39.80	58.95	4.6	13.76	.....
12	..	28	A	1	11/29/21	30.57	48.32	5.6	14.77	.....
12a	Same patient as No. 12				12/ 3/21	29.65	52.70	...	13.95	64.44
13	22	24	O	2	12/ 7/21	26.46	46.59	6.6	18.67	65.61
14	19	10	O	5	12/ 7/21	28.82	57.64	4.8	20.07	45.75
15	23	46	J	1	12/ 7/21	29.87	49.87	5.9	16.63	48.72
16	17	10	O	2	12/ 7/21	31.67	50.58	...	17.38	.....
17	24	52	O	3	12/ 9/21	17.40	42.42	4.6	16.28	46.46
18	22	18	O	1	12/ 9/21	21.29	45.10	5.23	13.15	38.62
19	23	38	J	1	12/ 9/21	25.45	57.64	5.6	17.64	38.62
20	19	24	O	1	12/ 9/21	25.69	54.17	6.6	21.29	49.48
21	23	38	J	1	12/ 9/21	24.65	47.37	5.35	14.46	41.64
22	20	20	C	1	1/25/22	33.85	57.28	2.7	15.21	65.17
23	19	20	C	1	1/25/22	29.15	63.63	6.17	26.07	30.77
24	18	8	C	1	1/25/22	32.38	62.03	4.2	20.58	84.49
25	24	6	C	1	2/ 1/22	25.95	53.24	1.94	14.21	98.98
26	18	24	O	1	2/ 1/22	25.72	53.31	4.88	34.70?	.....
27	38	72	C	6	2/ 1/22	14.86	44.28	4.97	17.96	.....
28	24	10	J	1	2/ 8/22	37.73	51.25	5.8	17.26	59.99
29	33	7	J	2	2/13/22	35.63	49.87	3.65	18.95	.....
30	22	24	O	3	2/15/22	24.47	55.99	7.34	20.98	53.39
31	17	24	C	1	2/15/22	23.25	44.73	6.43	23.66	23.39
32	25	7	It	1	2/15/22	30.48	58.44	4.13	17.40	77.38
33	24	24	O	...	3/24/22	22.91	58.93	5.67	19.36	.....
34	..	38	O	...	3/24/22	21.28	55.99	2.72	15.50	157.77
35	26	16	It	3	3/ 2/22	26.53	36.29	4.53	24.73	59.80
36	21	14	J	2	3/ 2/22	29.12	46.56	4.87	16.48	35.92
37	18	10	A	1	3/ 2/22	25.90	53.33	6.17	17.23	32.4
38	24	7	C	4	3/ 2/22	25.77	61.36	4.16	16.75	24.50
39	19	16	A	1	3/22/22	28.35	.....	8.77	19.60	.....
40	30	16	J	3	4/29/22	25.64	57.15	4.9	13.72	129.92
41	25	8	A	1	3/29/22	25.03	55.82	6.15	20.42	20.16
42	..	9	C	1	3/29/22	28.51	44.06	2.86	16.07	22.40
43	19	7	A	1	4/ 6/22	30.55	45.66	4.18	15.00	19.60
44	29	10	J	1	4/ 6/22	28.55	54.15	4.91	18.07	35.84
45	25	11	Sl	1	4/ 6/22	30.95	46.68	4.58	18.07	28.56
46	25	10	A	1	4/ 6/22	31.25	56.04	4.87	14.63	37.52
47	..	38	C	1	4/14/22	15.32	39.56	1.5	9.68	98.06
48	..	30	J	...	4/14/22	25.55	52.54	6.02	18.00	62.09
49	25	8	A	...	4/14/22	28.45	53.95	6.8	18.5	32.00
50	31	14	It	3	4/14/22	32.46	60.44	...	14.42	16.19
51	..	11	A	1	4/14/22	24.68	45.90	7.69	18.6	54.5
52	..	38	A	6	8/17/22	20.13	27.4	5.64	16.5	17.7
53	..	24	A	1	9/ 1/22	20.39	46.01	4.8	18.7	27.3
54	..	8	C	2	9/14/22	33.73	59.59	3.8	19.5	65.00

* C, colored; J, Jewish; It, Italian; A, American; Sl, Slavish.

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7. Kramer, B., and Tisdall, F. F.: J. Biol. Chem. **48**:1 (Sept.) 1921.

usually somewhat less sodium than is present in 0.5 c.c. of blood serum. When larger amounts of milk are used, this method should be applicable. The chlorids were determined by a slightly modified Volhard method. Probably a small percentage of the chlorids are lost in the ashing.

By inorganic phosphorus, we mean that obtained by the method of Bell and Doisy[8] on the filtrate after the addition of 20 per cent. trichloracetic acid to the fresh milk. According to Bosworth,[9] about 95 per cent. of the total phosphorus of human milk is in inorganic combination, and all of this is soluble. Our results do not agree with this finding. Like the same fraction in blood serum, the inorganic phosphorus increases somewhat as the milk ages. The greatest change that we have been able to obtain was from 6.3 to 7.9 mg. per hundred cubic centimeters of milk, or an increase of 1.6 mg. This change took place after the milk had been standing three days at room temperature. For total phosphorus, the milk was ashed with 0.5 c.c. of strong magnesium nitrate solution.[10] The ash was then taken up in water and dilute hydrochloric acid, to a volume of 50 c.c., and an aliquot part was determined by the method of Bell and Doisy. Blanks were, of course, run on the reagents.

TABLE 2.—*Comparison of Author's Results with Those of Others*

	Calcium*	Potassium	Inorganic Phos.	Total Phos.	Chlorids
Figures of Holt, Courtney and Fales†	33.7	47.6	....	15.0	35.45
Figures of German investigators‡	29.7	52.4	....	17.8	34.0
Authors' averages (white races)	30.79	50.38	5.45	17.33	43.79
Authors' averages (colored race)	25.41	53.18	4.8	18.01	57.02

* Constituents given in milligrams per hundred cubic centimeters of milk.

† The calcium, potassium and phosphorus are calculated from their figures for the oxid and are the averages of their "early mature and late mature" specimens which include milks from the end of the first to the end of the ninth month.

‡ Calculated from the oxid as above, including those specimens classified as "mature" milk.

Table 1 gives our complete results.

COMMENT

Table 2 shows that our results for the white races approximate very closely those of other investigators except as to the chlorids. The results as regards chlorids compare favorably with the results obtained by Sisson and Denis. The comparison of findings in the white races and in the colored race reveals differences in the calcium, inorganic phosphorus and chlorids. It has been shown that milk contains less inorganic material late in lactation, so this table would be of little value unless the average age of the babies of each group was known. The average age of the white infants was 16 weeks and of the colored, 22 weeks. Table 3 seems to show that the differences in the mineral content are not entirely due to the period of lactation.

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[8] Bell, R. D., and Doisy, E. A.: J. Biol. Chem. **44**:55 (Oct.) 1920.

[9] Bosworth: J. Biol. Chem. **20**:707, 1915.

[10] Bull. No. 107, Association of Agricultural Chemists.

Table 4 is included here to show a possible decrease in some of the inorganic constituents, particularly calcium, in the latter part of the winter and early spring, the time when rickets and tetany are most prevalent. The number of cases is not great enough to justify any conclusions.

In a study of the foregoing tables, several facts stand out which may be significant. The calcium content of the milk from colored women averages about 5 mg. per hundred cubic centimeters, or 17 per cent. less than that of the milk of all other races. This finding is consistent throughout, there being only three specimens from colored mothers in which the calcium content was more than 30 mg. per hundred cubic centimeters, the average for the white races. There were three values of less than 20 mg. and all were from colored women. If we take it for granted that negroes are more susceptible to rickets, this finding bears out the data collected by Bahrdt and Edelstein, who found the calcium considerably decreased in milk from mothers whose infants were rachitic.

Table 3.—*Comparison of the Inorganic Constituents of Human Milk at Different Periods of Lactation for the White and Colored Races*

Length of Period	Race	No. of Cases	Calcium	Potassium	Inorganic Phos.	Total Phos.	Chlorids
Less than three months...........	W	15	32.25	52.73	5.38	17.03	41.74
	C	9	29.07	54.37	3.93	16.21	56.69
From 3 to 6 months...............	W	4	29.11	47.76	6.06	18.81	37.3
	C	10	25.59	56.1	5.72	21.74	45.47
From 6 to 9 months...............	W	6	26.00	47.63	5.64	15.88	44.9
	O	5	21.67	48.29	4.52	13.79	86.57

Table 4.—*The Influence of Season on the Inorganic Constituents of Human Milk*

Period	Race	Calcium	Potassium	Inorganic Phos.	Total Phos.	Chlorid
From Nov. 9 to Jan. 31..........	W	33.12 (8)*	54.11 (8)	5.53 (8)	15.53 (8)	55.06 (5)
	O	26.4 (17)	54.06 (16)	5.27 (14)	16.74 (16)	51.16 (13)
From Feb. 1 to April 6..........	W	29.31 (15)	51.55 (13)	5.35 (15)	17.87 (15)	48.53 (13)
	O	22.69 (10)	51.15 (10)	4.24 (10)	19.89 (10)	62.33 (8)

* The numbers in parentheses are the numbers of cases from which the averages were computed.

The inorganic phosphorus averages about 12 per cent. less in the milk from colored women than in the milk from white women. There is more individual variation in the phosphorus content than in the calcium content, the milk of some of the colored women showing high results. Seven of the eight samples, however, having an inorganic phosphorus content of less than 4 mg. per hundred cubic centimeters came from colored mothers.

The chlorids averaged 30 per cent. higher in the milk from the colored mothers. There is again, however, a great individual variation. Unlike the other constituents, the chlorids averaged higher in late lactation than in midlactation. The tables of Holt, Courtney and Fales show this same result, but not to so marked a degree.

If it were possible to draw conclusions from this small series of cases, one might say that the breast milk most likely to produce rickets is characterized by a low calcium or inorganic phosphorus and a high chlorid content. It is quite possible that the sodium is also high in the cases with a high chlorid content. This combination is present in Cases 25, 34, 40 and 47. These were selected because all had a very high chlorid content. Three of these women were colored, and the other Jewish. In three, the inorganic phosphorus was very low. In the fourth, it was below the average for the race. The calcium of one was normal for that race. Two showed a calcium content about 16 per cent. lower than the average for the race and the fourth was 40 per cent. below. The infant in Case 40 had craniotabes, but no further evidence of rickets was obtained. The infant in Case 47 showed marked rickets clinically. The serum calcium and serum phosphorus were 7 mg. and 2.1 mg. per hundred cubic centimeters, respectively.

Only by rigid control of other factors would we be able to decide whether these figures have any real significance in the production of rickets. It is probable that an infant may develop rickets on breast milk of normal mineral content and that one may remain free from it on milk of an abnormal composition, as described above. Perhaps the differences noted between the white and colored races are due to inability of the colored mother to absorb the necessary actinic rays and has no influence on the production of rickets. This question is being investigated further.

CONCLUSIONS

1. A series of fifty-four specimens of human milk have been analyzed for calcium, potassium, inorganic and total phosphorus and chlorids. What might be termed micromethods have been employed in these analyses. The milk samples were collected without regard for the portion of the nursing. The averages of the results are practically the same as those reported by others who have used mixed or twenty-four-hour samples.

2. In comparing the white with the colored race, it was found that the calcium and the inorganic phosphorus were decreased in the milk from the latter race. The chlorids were considerably increased in the milk from the colored race.

THE ETIOLOGY AND TREATMENT OF HERPETIC (APHTHOUS AND APHTHO-ULCERATIVE) STOMATITIS AND HERPES LABIALIS *

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Herpetic stomatitis and aphthous stomatitis are considered by some authors as separate diseases and by others as the earlier and later stages, respectively, of one condition. From the different modes of presentation by the various authors, one gains, in reading the textbooks in different languages, the impression that uncertainty exists as to the cause of this disorder and as to the effectiveness of any one of the numerous therapeutic measures advised. Practically all authors agree that improvement takes place, more or less spontaneously, within from one to two weeks. Individual writers, however, point out that occasionally in poorly nourished individuals serious bowel disturbances will occur during the course of the stomatitis if the utmost care is not observed in improving the condition of the mouth.

From an etiologic standpoint, toxin absorption, direct bacterial action and poor personal and general hygiene, either alone or combined, have been blamed for the development of this type of stomatitis and for other types as well.

Various bacterial groups have been encountered in these cases, and were by some men associated with the development of the diseases in an etiologic capacity, only to be discarded by others. The same motley picture is presented in the recommendations for treatment, all of which, sooner or later, in most cases seem to bring about a definite improvement. This uncertainty as to the etiology and treatment of herpetic stomatitis indicates that the true etiology has not been recognized.

Recent clinical experiences have led us to believe that the underlying etiologic factor in these conditions is a disturbance of metabolism or nutrition; in other words, that any part that bacteria or similar agents may play in developing the different types of lesions is of a secondary nature.

Our first observation, which was followed by definitely planned methods of study, was made during the month of March, 1923. Two

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* The Babies' Dispensary and Hospital and the Department of Pediatrics, Western Reserve University and Lakeside Hospital.

* Read at the meeting of the American Pediatric Society, June 3, 1923.

sisters, one 11½ and the other 8¾ years of age, in a family of four children, in the best of hygienic surroundings, and apparently healthy—the one being 6 pounds (2,727 gm.) overweight, and the other up to average weight—developed on the mucous membrane at the base of the right lower canine tooth a group of small herpetic ulcers which caused distinct pain. No particular attention was paid to this until they complained in an emphatic manner regarding the annoying biting and stinging pain at meal time. Local treatment with a 3 per cent. solution of silver nitrate was given for forty-eight hours, without relief. It was then realized that as these children had not been eating oranges, except occasionally, these lesions might belong to the formes frustes of scurvy, as the diet which they were eating was very high in calories and adequate as far as the quantity and quality of the protein, fat, carbohydrate, minerals, iodin, fat soluble A and fat soluble D vitamins were concerned.

Accordingly, it was arranged to add the juice of two oranges to the diet and to drop all local therapy. The improvement was remarkably prompt and surprising. Within twenty-four hours, the patients experienced no more local pain and hardly knew whether the lesions were still present or not. On inspection, it was found that the small ulcers had lost their red boundary and had grown smaller. At the end of forty-eight hours, the lesions had entirely disappeared.

Two other patients, one of whom had in addition a severe aphthous stomatitis and Bednar's aphthae, were then treated in a similar manner, with a similar result. The patient suffering from aphthous stomatitis had been taking a tablespoonful of cod liver oil five or six times a week since last November. The other was rachitic and actively spasmophilic. The spasmophilia was uninfluenced by the orange juice therapy; in other words, just as in the case of the first patients, it was clear that the fat soluble A and fat soluble D vitamins had nothing to do with the production and cure of the stomatitis.

It was realized, however, that the only other vitamin, according to our present knowledge, that might be concerned in the development of this condition, was water soluble B. It was, therefore, decided that the influence of this vitamin would first have to be excluded before the conclusion could be reached that herpetic stomatitis belongs to the formes frustes of scurvy. Especially did this plan seem necessary and sound since it is known that (1) orange juice contains the water soluble B vitamin; (2) the deficiency of this vitamin in the diet brings about polyneuritis, and (3) herpes in its cutaneous form is considered a nervous system lesion.

Holt[1] makes the following pertinent statement in his chapter on aphthous, vesicular or follicular stomatitis: "We have adopted the term herpetic because the condition is analogous to herpes of the lips and face, the difference in appearance being due chiefly to location. It is apparently caused by something which acts upon terminal nerve filaments."

In order to determine the effect of the water soluble B vitamin alone on the stomatitis under discussion, yeast vitamin tablets were chosen as the therapeutic agent for the next cases. Each tablet contains 200 mg. of the standardized vitamin fraction, according to Osborne and Wakeman, is free from any living yeast cells, gives no protein reaction and is supposed to contain only the water soluble B vitamin. We had at our disposal some markedly scorbutic guinea-pigs prepared for some other work. In order to determine the freedom of the yeast vitamin tablets from any antiscorbutic power, these tablets were fed to four of these guinea-pigs. No improvement took place, and all died. The controls on orange juice recovered promptly. The antineuritic power of the yeast vitamin tablets was later tested as soon as pigeons which were at that time placed on rice and water diet developed marked signs of polyneuritis. The first four pigeons to be affected recovered on a dose of 1 tablet per os, three times a day. Thus, assurance was given that the yeast vitamin tablet was rich in the water soluble B vitamin and free from the water soluble C vitamin.

It is of interest that two of the polyneuritic pigeons, one of whom was in a stage of convulsions, were improved by the giving of orange juice (per os) in a concentrated form.

The first two cases (Cases 5 and 6) of herpetic stomatitis in which yeast vitamin tablets were given presented a severe stomatitis and gingivitis, with many herpetic and aphthous lesions. The second patient (Case 6) presented in addition a marked ulcerative stomatitis with offensive breath. Smears from the mouths of both patients were positive for Vincent's organisms. The second patient also presented a marked cutaneous herpes on the lips and at the chin. Both patients showed marked improvement within twenty-four hours and complete recovery within four days after receiving yeast vitamin tablets. The cutaneous herpes in the second of the two children yielded very readily to the yeast vitamin therapy.

This observation seems significant, as it suggests that possibly other forms of herpes, such as herpes zoster and the common herpes labialis, might have the same primary etiologic basis.

Since then, one case of herpes labialis and one case of herpes zoster inguinalis have been observed. The former occurred in a woman of

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[1] Holt, L. E.: Diseases of Infancy and Childhood, New York, The MacMillan Company, 1922, p. 276.

42 years, five days after the menstrual period. Twenty-four hours after the beginning of the yeast vitamin therapy (six yeast vitamin tablets, three times a day) all subjective symptoms had disappeared, and objectively the lesions were at a standstill. After forty-eight hours, there was evidently a definite regression in the lesions. The patient stated that ordinarily this degree of herpes would have given annoyance for from one to two weeks.

The herpes zoster inguinalis developed in a well-nourished young man of 30 years who had an excellent appetite and who was especially fond of bread. The herpes zoster was 48 hours old when yeast vitamin tablets were ordered, four tablets every three hours. After a lapse of forty-eight hours, the general symptoms of malaise and indisposition and the local symptoms of discomfort and pain were much improved; and at the end of the first week, the lymphadenitis which accompanied the herpes had disappeared and only pigmented areas at the seat of the former herpes remained. While cases of herpes zoster occasionally improve as rapidly with other therapy, usually from two to three weeks pass before the same stage of regression has been established. Further observations on a larger series of cases, of course, will be necessary before dependable conclusions can be reached regarding the value of yeast vitamin therapy in herpes zoster.

It is interesting to surmise what relationship the development of herpes labialis that occurs so frequently in cerebrospinal meningitis and pneumonia bears to this question of water soluble B vitamin supply and need.

It also seems important to point out here that the severe foul smelling ulcerative stomatitis in the second patient treated with yeast vitamin tablets (Case 6) improved rapidly and disappeared completely in a few days without any local therapy whatsoever, and evidently solely as the result of the therapy instituted. This observation together with similar observations made at a later date with other patients suggests that supplying the body of these patients with a sufficient amount of water soluble B vitamin eliminates the proper soil for bacteria, such as Vincent's organisms, which were found present in six of the cases of stomatitis so far observed. It seems probable, too, that noma and ordinary Vincent's angina are developed on this combined basis. In two of our cases, as a matter of fact, Vincent's angina was present, and in four others, as stated above, Vincent's organisms were found. It is planned to make definite studies in this connection.

The remaining six cases of combined herpetic, aphthous and ulcerative stomatitis, and one case of acute gingivitis all had similar records of recovery. In two of these cases, however, a persistent constipation seemed to limit the degree of effectiveness of the yeast vitamin tablets.

as a rapid improvement was again instituted following the administration of a cathartic. That constipation plays no primary rôle in the development of herpetic stomatitis is clear from the fact that, in all other cases, no history of constipation could be elicited.

The following histories present in detail data of interest in the study of these cases:

Case 1.—*History.*—R. S., girl, aged 11½ years, height 58 inches (243 cm.), weight 93 pounds (42.0 kg.) was according to school schedule 6 pounds (2.7 kg.) above average weight. Her home conditions were excellent in every respect. She had had mumps, measles, chicken-pox, whooping cough, influenzal pneumonia and, one year previous to examination, tonsillitis followed by nephritis. Before the last illness, she was underweight and, therefore, a diet liberal in calories and supposedly complete was ordered, which resulted in a distinct gain in weight.

The general condition and nutrition were excellent, as was the condition of the teeth. The diet was as follows:

Breakfast: Simple cereals in liberal amounts with sugar and milk, toast, and 8 ounces (236 c.c.) concentrated liquid S.M.A. (synthetic milk adapted) to drink.

Dinner: Either meat or eggs, potatoes and one other vegetable—spinach, carrots, beets, beans, peas, cauliflower, occasionally lettuce and canned tomatoes, i. e., about once every ten days. The spinach, carrots, beets and potatoes were as fresh as they are purchased in the city of Cleveland at any grocery store. Apple sauce and bread and butter were given daily; occasionally with jelly; and 8 ounces of pasteurized milk.

After school lunch: Eight ounces of concentrated liquid S.M.A., two or three plain or graham crackers, one apple daily, and occasionally one orange.

Supper: Eight ounces of pasteurized milk, four pieces of zwieback, and pudding or jello, etc.

The child was seen, March 14, 1923. For the past few weeks, she had been bothered by small sores on the inner side or bottom of the left lower lip. They were very annoying because when they were touched, especially by the tongue, a sharp stinging pain resulted.

Examination.—On the mucous membrane at the base of the right lower canine was a group of three or four herpetic ulcers. The individual lesions were surrounded by a narrow bright red areola.

Treatment.—Silver nitrate 3 per cent. was employed locally once daily. Diet was continued the same.

Course.—March 15: There was no subjective or objective improvement. Silver nitrate was again applied.

March 16: Silver nitrate was discontinued, and the juice of one orange was ordered, to be taken twice daily.

March 17: The patient reported that the lesions gave her no more pain and was in doubt as to whether they still existed or not. Examination showed them reduced in size and the red areola gone.

March 18: Patient made no complaint. On inspection there was no evidence of ulcers.

Summary.—A well-developed and healthy looking girl, living in excellent surroundings, 6 pounds over average weight, taking a high caloric diet, adequate in protein, fat, carbohydrate, minerals, fat-soluble A and fat-soluble D vitamins (cod liver oil in the form of S. M. A.), and including a daily intake of vegetables and apples developed a simple herpetic stomatitis, which did not improve under local therapy (silver nitrate), but which was relieved in twenty-four hours or less by the addition of 2 ounces of orange juice to the diet, and in forty-eight hours was entirely healed.

Case 2.—*History.*—L. S., girl, sister of the patient in Case 1, aged 8¾ years, height 52 inches (131 cm.), weight 63½ pounds (29 kg.), the average weight for girls for the age and height, had the same home conditions as the patient in Case 1. Her general nutrition was good, being better than at any time during the last four or five years. The condition of the teeth was excellent.

The patient had had mumps, measles, chicken-pox, whooping cough and influenzal-pneumonia. She had been of a nervous temperament since the second year.

The diet was exactly the same as in Case 1, except that beef oleomargarin was used more frequently than butter.

The complaint was the same as in Case 1, except that the condition apparently had developed a little earlier. In addition, the parents noticed that the child was even more restless during the night than usual, and she occasionally complained of severe abdominal pain, for which no explanation could be found.

Examination.—An exactly similar condition was found in the same location as that in Case 1.

Treatment.—This was the same as that given in Case 1, with exactly the same results. After orange juice was added to the diet, this patient slept much more quietly and did not complain of abdominal pain.

Summary.—A girl, aged 8¾ years, of neurotic type, living in excellent surroundings, in a better state of nutrition than she has been for a number of years, and taking a high caloric diet, adequate in protein, fat, carbohydrate, minerals, fat-soluble A and fat-soluble D vitamins (cod liver oil in the form of S. M. A.), and including a daily intake of a variety of vegetables and apples, developed simple herpetic stomatitis, which did not improve under local therapy (silver nitrate) but in twenty-four hours or less after the addition of the juice of two oranges daily to the diet no symptoms and in forty-eight hours was entirely healed. Restless sleep and abdominal pain disappeared.

Case 3.—*History.*—H. S., woman, aged 22, in a good state of nutrition although somewhat underweight, had the same home conditions as those in Cases 1 and 2. The past history was of no consequence except that the patient occasionally had cold sores. The general condition and nutrition were from fair to good. The condition of the teeth was excellent.

The diet was the same as that in Cases 1 and 2, except that the total intake of milk for twenty-four hours was limited to 1 pint (0.5 liter) of ordinary pasteurized milk. One tablespoonful of cod liver oil was taken five or six times a week through the entire winter.

March 29, the patient complained of rawness of the surface on the inner right lip, causing a stinging, biting pain, especially when touched.

Examination.—On the mucous membrane of the lower lip, on the right side near the base of the gums, was a group of herpetic ulcers.

Treatment.—The juice of one orange, twice daily, was ordered, but the order was not carried out until the following day. According to the report from the patient, the pain disappeared soon after the juice of the first orange was taken.

On the following day, March 31, even though the local soreness of the lip had disappeared, the throat became sore and the patient felt tired. April 1, she went to bed thinking that she had an ordinary sore throat. April 2, she presented a Vincent's angina, which was corroborated by bacteriologic examination.

Potassium chlorate was ordered internally and as a mouth wash, and the patient improved, the throat being free from exudate, April 4. No special significance was attached to the development of Vincent's angina at that time.

The diet consisted of soups, milk and toast during her illness. The patient cannot recall how much orange juice was consumed at that time.

Summary.—A somewhat under-nourished woman, aged 22, living in excellent surroundings, and on a diet seemingly of sufficient caloric value and adequate in protein, fat, carbohydrate, minerals, fat-soluble A and fat-soluble D vitamins, including a daily intake of vegetables and apples, developed a herpetic stomatitis which improved within twenty-four hours on administration of orange juice, but was followed, within a few days, by development of Vincent's angina.

It should be noted here that the apples and potatoes used in the diets of the three patients just considered were placed in the vegetable cellar during fall in sufficient amounts to last the entire winter. The apples had somewhat shriveled since February. Whether the storage conditions for the potatoes were ideal or not it is difficult to say.

Case 4.—*History.*—M. D., boy, aged 15 months, weight 9,290 gm., temperature 38.2 C. (100.6 F.), was slightly underweight although his layer of adipose tissue was good. The home conditions were fair. The residence was located in one of the poorest sections of the city.

The birth weight was 4 pounds (1,814 gm.). The patient had been breast fed for two weeks, and was then fed a simple milk dilution. One month after birth, he had a fever whose cause was not discovered. He had never been ill until the present time, and had had a good appetite.

The general condition and nutrition were from fair to good. The patient was only slightly under weight. The condition of the teeth, four in number, was good. There was no caries. The appetite had been excellent until the present illness. The patient was especially fond of potatoes and bread. He took nearly 1 quart (liter) of milk daily. No oranges and very little vegetable food were given him.

There had been sores in the mouth and on the lips for twenty-four hours. The baby did not want to eat, and he drooled a great deal.

Examination (April 11, 1923, at the Babies' Dispensary and Hospital).—There were irregularly shaped ulcers on the tongue and also at the sides of the palate (Bednar's aphthae). The spleen was palpable. The epiphysis was enlarged at the wrists and a rosary was present. A diagnosis of aphthous stomatitis and rickets was made.

Treatment.—Boroglycerin was applied to the mouth, four times a day. Cod liver oil with calcium phosphate (1 dram), three times a day, was prescribed. The diet was that usually given children 15 months to 2 years of age.

Course.—April 12: The mother reported that child had not urinated since yesterday. The mouth condition was practically unchanged.

An examination showed that the gums were red and somewhat swollen. The ulcers on the tongue were more numerous and those on the soft palate larger. The drooling had increased. The urine showed an occasional cast and a trace of albumin. The patient was sent to Lakeside Hospital for ward care.

On admission, April 12, the former findings were confirmed. The serum calcium was 7.0; serum phosphorus, 3.8. There was spasmophilia, with a positive facial and Trousseau signs, and laryngospasm.

Examination of the urine revealed a slight trace of albumin and an occasional red cell; the benzidin test was positive.

Cow's milk was prescribed (200 c.c., six times a day).

April 13: The patient took only 430 c.c. of milk.

Examination revealed no change, except that the spasmophilia signs were distinctly less active. Two hundred cubic centimeters of milk, six times a day; three zwieback twice a day, and 30 c.c. of orange juice four times a day, were given.

April 14: The infant took only 375 c.c. of milk and would not take the zwieback. The spasmophilia was the same. The local condition of the mouth was definitely better (redness and swelling less; ulcers smaller). The same diet was ordered.

April 15: The patient took 725 c.c. of milk and all of the zwieback ordered. The spasmophilia was the same. The local condition was markedly improved (ulcers on tongue and buccal and labial mucus membrane almost gone; Bednar's aphthae much reduced in size). The child was happier. The urine contained much mucus, and was stringy. The benzidin test was negative.

April 17: The patient took 875 c.c. of milk and all of the zwieback. The spasmophilia was worse. The facial phenomenon was 2 + and the laryngospasm was definite again. Only slight pits at the seat of the ulcers could be seen. Bednar's aphthae were markedly reduced. The same diet was ordered.

April 18: The patient took 1,050 c.c. of milk and all of the zwieback. The spasmophilia was unchanged. The mouth was practically healed. The same diet was ordered.

April 19: Examination of the mouth was negative. The spasmophilia was unchanged. The capillary test was 2-3.

Summary.—A well nourished rachitic and decidedly spasmophilic infant living in fair surroundings, who developed a marked aphthous stomatitis, including Bednar's aphthae, was rapidly relieved of his stomatitis by the administration of 30 c.c. of orange juice four times a day. The stomatitis showed a distinct improvement twenty-four hours after administration of orange juice was started, and a remarkable change for the better at the end of forty-eight hours. The spasmophilia was unchanged.

CASE 5.—*History.*—N. K., girl, aged 17 months, weight 9,350 gm., temperature 37.3 C. (99 F.), whose home conditions were fair (residence located in poor district of city), weighed at birth 7¾ pounds (3,196 gm.). She had never been acutely ill. She was undersized and underdeveloped, but was fairly well nourished. There were no signs of rickets; and the teeth were not carious.

The child was breast fed three times a day (evidently, a very small amount). The appetite was good until illness developed. No orange juice and no cod liver oil had been given. The child took from 1 to 1½ pints (500 to 750 c.c.) of milk and, according to parents, "eats everything just like us." She was especially fond of potatoes and liked bread. Only a small amount of vegetables was taken. April 16, the baby complained of a sore mouth.

Examination (April 16, at the Babies' Dispensary and Hospital).—The baby was under sized and pale. She drooled, and the tongue and gums were swollen and fiery red, and bled easily. On the tongue were many herpetic and aphthous lesions. These were also found on the under surface of the tongue and the inner side of the lips.

April 17: The condition of the mouth was worse. The gums were decidedly inflamed not only about the incisors, but also about the bicuspids. The condition was different from the swelling and discoloration seen in scurvy. The tongue was red and swollen and covered with herpetic and aphthous lesions. Smears were made which, according to the report from Dr. B. S. Kline (department of pathology, Lakeside Hospital), warranted a diagnosis of an infection with Vincent's organisms. Capillary test was 2-3.

Treatment.—Two yeast vitamin tablets (No. 960) containing each 200 mg. of standardized vitamin fraction, were prescribed, three times a day. No orange or tomato juice was given, the diet being unchanged.

Course.—April 18: The father maintained that the child was distinctly better. Four tablets were given, April 17, and two, April 18 in the morning. Improvement was noticed when child arose; that is, before the fifth and sixth tablets were given. The father was positive that child was getting no orange juice. The mouth showed a decided improvement. Color and swelling of the gums were improved and the herpetic lesions were cleaner and less fiery.

April 19: The father reported the baby much better, eating and sleeping better, and "cheeks him red again." The baby took all the tablets and much more food and milk. No orange juice was given.

The improvement was remarkable. The herpetic lesions were replaced by circular, pale, flat, mild-looking areas. The gums were pink and only slightly swollen at the upper and lower incisors. There was no bleeding. The child was contented and opened the mouth without objection. There was a decided improvement in the general condition, especially in her color. The treatment was continued.

April 20: The mother brought in the child, which was happy, talked continually, and looked well. There was only a slight indication of the presence of the old lesions. The gums were normal except at the right upper and left incisor, where a very slight redness and swelling was present. Treatment was continued.

April 23: There were no symptoms. The condition was excellent. The regular diet was ordered, with the juice of either one orange or one tomato daily.

Summary.—A 17 month old girl, small but fairly well nourished, in poor surroundings, eating a mixed diet, including 1 to 1½ pints of milk and emphasizing potatoes and bread, developed a severe herpetic and aphthous stomatitis and fiery red gingivitis, which improved distinctly within twelve hours after the administration of yeast vitamin. Within thirty-six hours, the improvement was remarkable, and within sixty hours healing was practically complete. No local nor antiscorbutic therapy was instituted. Smears warranted the diagnosis of a mild Vincent's infection.

Case 6.—*History.*—I. G., girl, aged 2 years, weight 12,600 gm., temperature 38 C. (100.4 F.), whose home conditions were fair, weighed at birth 9½ pounds (4,096 gm.). She was breast fed for one month and then whole milk (3 parts) and water (1 part) was given for six months. Later, milk alone with the cream removed was given. The baby had never received cod liver oil, and orange juice, prune juice or tomato juice only rarely and in small amount. During the fall of 1922, she had a discharging ear. She walked at 15 months. The general condition and nutrition were good. The teeth were not carious.

The baby took four or five bottles of pasteurized milk (8 ounces) daily. She ate a great deal of bread and potatoes, but no cereals or vegetables. Although the mother offered her orange juice, the child refused it.

Since April 15, the child has not been well. April 16, sore mouth and fever were noted, and the patient had no appetite. April 17, there were sores on the lips and chin.

Examination.—The child was well developed and well nourished. There were herpetic lesions on the left upper lip near the center and at the angle of the mouth; also a conglomerate mass of herpetic lesions the size of a quarter at the point of the chin. The tongue was swollen and red, and covered with numerous herpetic and aphthous ulcers, of which a few were on the hard palate and on the inner surface of the lips and cheeks. The gums are inflamed, bright red and bleeding.

Treatment.—Orange juice, two times a day, was prescribed, and a diet suited for a 2-year old child was ordered.

Course.—April 19: The child's temperature was 37 C. (98.6 F.). The mother reported that the child violently objected to taking orange juice, and she doubted that any was swallowed. The baby was no better; in the opinion of the mother, it was worse. There was a foul odor from the mouth. Examination revealed a typical cutaneous herpes on the central and lateral portion of left upper lip and chin. The child objected to inspection of mouth. The tongue was covered with irregularly shaped aphthous ulcers on the left side and a large number of herpetic areas on the other side. The whole tongue was swollen, red and sore. The gums were markedly swollen, and bright red except about the upper and lower incisors, where they were bluish. They bled easily. At the junction of the gums and teeth, a yellowish seam of purulent material was present, covering the small ulcers. Behind the front teeth of the upper jaw, much viscid purulent material was present in a layer from 2 to 4 mm. wide. There is marked fetor ex ore. The capillary test revealed a distinctly increased permeability. Petechial spots appeared within two minutes after the cuff was applied.

Two yeast tablets containing 200 mg. each of standardized vitamin fraction were given three times a day. The diet was unchanged, except for the omission of orange juice.

April 20: The mother succeeded with great difficulty in getting the child to take about 3½ or 4 tablets during the night. There was apparently some improvement in the condition. The tongue was somewhat less inflamed and the aphthous and herpetic areas had less redness about them. There was no change in the herpetic lesions on the skin. Smears from the various lesions stained by Dr. B. S. Kline showed typical and numerous fusiform bacilli and a few typical spirilla of Vincent's.

The child was sent to Lakeside Hospital for observation and treatment. On admission (4 p. m.) the following treatment was ordered: 8 ounces of pasteurized milk, five times a day; two yeast tablets containing 200 mg. each of standardized vitamin fraction, four times a day.

April 21: At 8 a. m., the child had taken 750 c.c. of milk and six yeast vitamin tablets No. 960 since admittance. The nurse reported improvement. The herpetic lesions on the lips and cheeks seemed "shrivelled up," and presented a marked improvement. The tongue was less inflamed; the herpetic lesions on the left side of the tongue were decidedly smaller and the aphthous ulcers were reduced in size and less inflamed. The gums were less swollen and the child had a different facial expression, appearing more comfortable. Eight ounces of milk, five times a day, and two yeast vitamin tablets (No. 960), four times a day, were ordered.

April 22: The child took 790 c.c. of milk and all of the tablets.

Improvement was very marked. The thick layer of pus behind the upper incisors was much reduced in amount. The aphthous ulcer pits were filling in from the bottom and narrowing in from the sides. The gums were much improved, and the herpes on lips and chin was dried up. The treatment was continued unchanged.

April 23: The child took 975 c.c. of milk and all of the tablets, and seemed to be hungry. Improvement continued. Fetor ex ore was much less. The treatment was the same, plus two pieces of zwieback, three times a day.

April 24: The child took 1,150 c.c. of milk, all the zwieback and the tablets. The pus behind the upper incisors was gone, and there was no fetor ex ore. Minute pits of the deep aphthous ulcers remained. The gums at the upper central incisor were still somewhat swollen and bluish red (scorbutic?).

April 25: Cure was complete except that the gums about the central upper incisors were still blue and somewhat smaller. Pigmentation was still present at the former seat of the herpes on the lips and especially on the chin. The same diet was ordered, but the yeast vitamin tablets were replaced by 15 c.c. of orange juice, to be given four times a day.

April 26: There was a slight improvement in the condition of the gums. The treatment was continued.

April 28: The gums were distinctly paler and reduced, and seemed normal (scorbutic?).

Summary.—A well nourished girl of 2 years, with a severe herpetic and aphthous and foul smelling ulcerative stomatitis of two days' standing, accompanied by the presence of a cutaneous herpes on the lips and chin, after forty-eight hours of unsuccessful attempts at home to administer adequate amounts of orange juice and yeast vitamin tablets, was admitted to the hospital, where the administration of yeast vitamin tablets produced a remarkable improvement within eighteen hours in the skin, mucus membrane and lesions. The rapidity and degree of the improvement however, was in all probability partly due to the four tablets which the mother succeeded in giving the child during the previous night.

This remarkable improvement did not include in the same degree the gums about the upper central incisors, whose discoloration was more of a bluish than of a bright red tint. The administration of orange juice seemed to result in an improvement, and it may be that a mild scurvy might have been responsible for this localized abnormality. Smears showed the presence of Vincent's organism.

Case 7.—*History.*—R. S., a Syrian girl, aged 18 months, weight, 10,160 gm., temperature 37.5 C. (99.5 F.), admitted to Babies' Dispensary and Hospital, May 8, 1923, and whose home conditions were poor, had been treated for nasopharyngitis at the age of 3 months and had otitis media at the age of 15 months. The general condition and nutrition were good. The teeth were not carious. The baby still took the breast, but got very little, according to the mother, and ate "everything," especially potatoes, until four days before admission. The mother stated that for two months the child had been given one orange daily. For four days, the baby had had sore mouth, had been feverish, could not eat and was restless during the night.

Examination.—She was a rather well-nourished child, showing on tongue. buccal mucous membrane and soft palate many herpetic and aphthous ulcers. The gums were swollen and bright red. There was much salivation.

Treatment.—Two yeast vitamin tablets No. 983, every three hours, were ordered, the diet to be unchanged if appetite returned.

Course.—May 9: The mother reported that the child slept well for the first time since it had been sick. Since morning, she had had better appetite. The bowels had not moved for two days. The general redness of the oral mucous membrane was improved. The inflammatory condition was better, and the ulcers showed slight improvement. No new lesions were present. Yeast vitamin tablets No. 983, two tablets every three hours, were continued, and an enema given.

May 10: The mother was gratified at the baby's improvement, reporting that she played, did not cry and slept well. The bowels had not moved for three days. In addition to crackers, oatmeal, mashed potatoes and milk, the child had taken twelve tablets. The gums were still slightly swollen. The herpetic lesions on the lower lip and left buccal mucus membrane were practically gone. The small lesions on the tongue were reduced and less inflamed, as were also the herpetic lesions on the soft palate. Five tablets each of No. 960 and No. 983 were prescribed.

May 11: The temperature was 37 C. (98.6 F.), and there was a great improvement. The bowels moved after a laxative was given. The ulcers on the soft palate were practically gone. A few ulcers were still present on the buccal mucosa. Two tablets (No. 983), four times daily, were ordered.

May 14: The child was in excellent condition, all lesions being healed except for slight evidence of ulcer remaining at tip of tongue.

Summary.—An 18-month-old Syrian girl, fairly well nourished, in poor hygienic surroundings, still getting some breast milk and eating "everything" but especially potatoes and supposedly getting during the last two mouths before illness one orange daily, developed a severe herpetic and aphthous stomatitis and gingivitis, all of which distinctly improved after the first twenty-four hours of yeast vitamin administration in doses of approximately twelve tablets a day. The improvement was marked during the first night even though the bowels had not moved. The greatest improvement occurred after the second twenty-four hours, during which bowel evacuation occurred. Some doubt exists as to the reliability of the statement regarding orange juice administration. It is conceivable, also, that the water soluble content of the oranges was low.

Case 8.—*History.*—M. S., a Syrian girl, aged 10 years, temperature 37 C. (98.6 F.), older sister of patient in Case 7, admitted to the Babies' Dispensary and Hospital, May 14, 1923, and whose general condition and nutrition were good, and condition of teeth bad (marked caries), ate everything, especially potatoes and bread, and took from one to two glasses of milk daily, but was given little meat and vegetables and no oranges. The appetite was good. For six days, she had been in bed with severe sore mouth, drooling a great deal and in great pain. She had taken a cathartic during the past two days and was some better than two days before, but still felt sick and did not care to eat. There was a bad odor from the mouth.

Examination.—The patient was a well nourished girl with a markedly inflamed mouth, having herpetic lesions at the tip of tongue and on the buccal mucous membrane. The gums were markedly inflamed and fiery looking, especially so about the many decayed teeth whose gums at the junction with the teeth are covered with a fine purulent exudate. The gums bled easily. There was fetor ex ore. A smear stained by Dr. B. S. Kline showed numerous typical fusiform bacilli and a few typical spirilla of Vincent's.

Treatment.—Two yeast vitamin tablets No. 983, every two hours, were ordered.

Course.—May 16: There was marked improvement of all the lesions. The child had distinctly less pain and could eat. She had noticed improvement the day before.

The ulcers were practically gone. Gingivitis was still present but much improved. Fetor ex ore was no longer present. Two yeast vitamin tablets No. 983, five times a day, were ordered.

May 18: The mouth condition was excellent. The patient had no pain, and the appetite was good. No ulcers could be seen, and the gingivitis was gone except about teeth having marked caries, where it was present to a slight degree.

Summary.—A girl, 10 years old, quite well nourished, with marked dental caries, developed a severe herpetic stomatitis and acute ulcerative gingivitis, which after six days improved remarkably, within forty-eight hours after administration of yeast vitamin tablets. Within four days, the ulcers disappeared and the gingivitis improved remarkably.

Case 9.—*History.*—R. F., boy, aged 7 years, admitted to Lakeside Dispensary, May 16, 1923, whose home conditions were poor, had had pneumonia two years previously, and occasionally had sore throat. His general condition and nutrition was fair. The teeth were poor, being markedly carious.

Until the present illness, his appetite was fine. He ate a "lot of potatoes" and also liked bread and butter. He did not care for vegetables and got no oranges. Canned tomatoes were eaten rarely. A small amount of meat was taken once daily, and very little milk.

A "canker sore" had been present for one week, with fever. The patient had eaten nothing, and had gargled with salt and Epsom salt water. The white sores had somewhat improved, but the fever still persisted, and the patient refused to eat. Two days previously, he had gone to Lakeside Hospital Dispensary, where orange juice and a soft diet were ordered. The child took only a small amount of orange juice, however, and he still would not eat. There was drooling, and sleep was restless.

Examination.—The patient was a somewhat undersized but fairly well nourished boy, showing markedly inflamed, swollen and reddened gums with herpetic ulcers on the tongue and buccal mucus membrane. There was marked fetor ex ore.

Treatment.—Yeast vitamin tablets No. 983, four every three hours, were ordered, but no orange juice.

Course.—May 17: The child rested better during the night. He was given twelve tablets before retiring. He ate breakfast and, according to the mother, was like a different person, and felt better than he had since his mouth became sore.

Yeast vitamin tablets No. 983, two every four hours, were ordered.

May 18: Mother and boy were both very sure about improvement. The boy did not complain, and played and ate. The ulcers were distinctly smaller and very superficial. The gums were still inflamed but were better. During the night, there was slight bleeding from the mouth. Yeast vitamin tablets No. 983, two every four hours, were ordered.

May 19: The condition was unchanged. A small amount of pus could be squeezed from under the gums by pressure. The gums were still somewhat swollen and red. A foul breath could also be noticed.

May 21: There was no more bleeding. The child ate all the food ordered, and was subjectively completely well. There was a decided improvement. The gums were very firm and only a small amount of pus was obtainable by pressure. Yeast vitamin tablets No. 983, two every four hours, were prescribed.

May 23: Mouth could be considered cured.

Summary.—A 7-year-old boy living in poor surroundings, somewhat undernourished, suffering from herpetic and aphthous stomatitis and ulcerative gingivitis, after a continued illness of a week or more with but little improvement, showed within twenty-four hours after yeast vitamin administration a distinct improvement and within one week a complete cure. Especially subjectively were the tablets of decided and early value.

CASE 10.—*History.*—B. S., a girl, American, aged 1 year, admitted to the Babies' Dispensary, May 15, 1923, lived under fair conditions at home. She was occasionally constipated. She had been breast fed entirely for from seven to eight months; was weaned at 11½ months, and since then 1 quart (liter) had been given of cow's milk daily, with no additional food and no orange juice. She had had a sore mouth and throat for four days, was restless and fretful, and could be fed only with a spoon. A laxative had been given two or three times during the past few days.

Examination.—The child was well developed and quite well nourished, weighing 8,420 gm. The temperature was 39.2 C. (102.6 F.). There were small herpetic lesions on upper and lower lips. The gums were bright red and swollen. Herpetic ulcers were present on the mucous membrane of the cheeks, tongue and lips. The tonsils were covered with brownish-gray exudate. The child had a rosary with sharp edges. The extremities were not sensitive.

One quart (liter) of milk daily, and two yeast vitamin tablets No. 983, two every three hours, were ordered.

Course.—May 16: The child had fever all night and coughed a great deal. A smear made from the tonsils stained by Dr. B. S. Kline showed many fusiform bacilli and a few spirochetes. The temperature was 38.4 C. (101.1 F.). Yeast vitamin tablets No. 983, two every three hours, were ordered.

May 17: The child was better. Culture from the tonsils was negative to diphtheria. The condition of the tonsils, ulcers on the tongue and lip and herpetic lesions on the lip improved but the condition of the gums seemed unchanged. The temperature was 37.2 C. (99 F.). Yeast vitamin tablets No. 983, two every three hours, were ordered. Because of the type of rosary and persistence in the swelling of the gums, 1 ounce (28 c.c.) of orange juice, four times daily, was ordered in addition.

May 18: All symptoms were improving. The child refused milk. The tonsils were much improved, as were the ulcers and gums.

May 21: There were loose stools and fever. The patient did not look sick. The tonsils and mouth were free of lesions. The tablets were discontinued.

Summary.—A 1-year-old child, with severe herpetic stomatitis, acute and severe gingivitis and a Vincent's angina, improved decidedly within forty-eight hours after the administration of yeast vitamin tablets. Because orange juice had not been a part of the diet, and because of the less ready improvement of the gums and the suggestive rosary, orange juice was ordered on the third day of yeast vitamin administration, on the assumption that scurvy also might be present. The next day brought an improvement in the condition of the gums. Whether or not this was due to the antiscorbutic power of the orange juice it is impossible to say.

Case 11.—*History.*—C. W., girl, Jewish, aged 2 years and 5 months, weight, 13,980 gm., admitted to the Babies' Dispensary, May 21, 1923, whose home conditions were very poor, but whose general condition and nutrition were excellent and condition of teeth good (no caries), until the present illness had been eating "everything" and drinking one quart (liter) of goat's milk daily. She was given a large amount of potato, and some cereal and bread and butter, but no orange. She had had sore mouth for a day; would not eat; slept poorly. There was no constipation.

Examination.—The patient was a well-nourished, chubby, strong child that vigorously objected to having its mouth examined. Three herpetic ulcers were found on the tip of the tongue; two on the inside of the upper lip. Both upper and lower gums were decidedly swollen and red, and bled easily and markedly. The extremities were not sensitive to pressure.

Treatment.—The diet was continued as before. Yeast vitamin tablets No. 983, four every three hours, were ordered.

Course.—May 22: The child had a restful night and ate this morning. The sister stated that there was a distinct improvement. The herpetic ulcers were distinctly better. The gums were paler and bled less readily, but were still swollen. Yeast vitamin tablets No. 983, four tablets every three hours, were continued.

May 24: The child did not return to the dispensary as ordered, so a visit to the home was made. The patient was eating bread. The ulcers on the tongue could hardly be seen. The gums, however, were still swollen, and bled during the examination. It was ascertained that during the past thirty-six hours the child had received no tablets. The mother promised to carry out orders.

May 25: The child was distinctly better, but the gums still bled some. The bowels had been moving one or two times daily. The ulcers on the tongue could not be seen. The gums were better but were still somewhat swollen and somewhat bluish red. Bleeding was distinctly less. Yeast vitamin tablets No. 983, three every three hours, were ordered. The mother stated that it had been difficult to give the child the tablets and occasionally she succeeded in spitting them out.

May 26: The sister stated that the child was much better. The gums were distinctly improved and bleeding at examination was very slight.

Summary.—A healthy looking, vigorous girl of 2 years and 5 months of age, on a liberal diet, developed acutely herpetic stomatitis and severe inflammatory gingivitis. A decided improvement was brought about in twenty-four hours in the condition of the ulcers by the administration of yeast vitamin. Within forty-eight hours the small ulcers practically disappeared. The gums were improved, but not to the same degree. After better cooperation in the home, the gums also improved distinctly.

Case 12.—*History.*—N. S., boy, aged 5 years, height 46½ inches (116 cm.), weight, 53¼ pounds (24.2 kg.), whose home conditions were good, and whose general condition and nutrition were excellent, although the teeth showed some caries, ate "everything," but especially potatoes and was also very fond of butter and bread. He drank no milk, and ate one banana daily, but no oranges. For the past two days, fever and malaise had been present and for one day sore mouth. Fever had been present the previous night, and the boy would not eat.

Examination.—The patient was well developed and well nourished. There were herpetic ulcers on the buccal mucous membrane and tongue. The submaxillary and postcervical glands were enlarged. The temperature was 37.5 C. (99.5 F.).

Treatment.—Yeast vitamin tablets No. 983, four every three hours, were ordered.

Course.—May 22: The child felt better, ate breakfast and played. The ulcers were smaller and showed less inflammation.

May 23: There was no improvement over the day before. The bowels had not moved for three days. The condition of the ulcers and glands was unchanged. Yeast vitamin tablets, two every three hours, and castor oil 1 tablespoonful, was ordered.

May 24: The boy was better. The bowels moved in the morning, but improvement was apparent before. The patient ate well. The ulcers were healing and diminishing, and the glands were smaller. The patient acted as if he were better.

May 25: The patient's condition was excellent. He ate well and played. Marked improvement of buccal ulcers was noted. The lymphatic glands were distinctly smaller and the gums paler. The treatment was continued unchanged.

Summary.—A very well developed and well nourished boy of 5 years developed an acute herpetic stomatitis with fever and lymphadenitis. A decided improvement was produced in the general condition of the child and the local state of the ulcers within twenty-four hours by administration of yeast vitamin. After the second twenty-four hours, this improvement ceased abruptly. After another twenty-four hours, during which, in addition to the yeast, a cathartic was administered to bring about intestinal evacuation, which had not occurred for three days, improvement was again apparent. What rôle the cathartic played herein, it is difficult to say. That it was not the sole cause for the improvement is clear from the observation of the mother that the child felt improved before the bowels moved. Another twenty-four hours showed a decided reduction in the ulcers and size of the lymphatic glands.

Case 13.—*History.*—R. T., a girl, aged 22½ months, mulatto, weight 11,930 gm., whose home conditions were fair, and whose general condition and nutrition were good, and condition of teeth excellent, admitted to the Babies' Dispensary, May 23, 1923, had been eating "everything," including three glasses of milk and a liberal quantity of potatoes. She had also been getting some orange juice, rarely, and prune juice. The patient's mouth had been sore for the past week, and the appetite was poor.

Examination.—The patient was a well-nourished, vigorous girl, with markedly swollen and bright red gums, which bled easily. No ulcers were present. The temperature was 37 C. (98.6 F.).

Treatment.—The diet without orange juice, was unchanged, and yeast vitamin tablets No. 983, four every three hours, were ordered.

Course.—May 24: The mother stated that the child was better. She slept better during the night and ate and acted better during the morning. The bowels had been moving regularly two or three times daily, even before the child got sick. The gums were much improved. Only those between the central and lateral incisors above and below were still somewhat swollen. Three yeast vitamin tablets No. 983, four times a day, were ordered.

May 25: The mother stated that the baby was "ever so much different," and played and ate well. The gums were normal, except between the lower central incisors. Administration of the vitamin tablets was continued.

May 26: The mother stated that the child's improvement continued and that she seemed well. There was only very slight swelling of the gum at the left lower lateral incisor.

Summary.—A rather severe gingivitis in an active, strong well nourished child of 22½ months was bettered within twenty-four hours and much improved within forty-eight hours as a result of yeast vitamin administration.

COMMENT

It is evident that the administration of the water soluble vitamin B had a remarkable therapeutic effect, not only on the herpetic stomatitis in its pure form, but also on aphthous and ulcerative stomatitis as well, and in two cases of herpes labialis.

The children, on the whole, have been close to normal in weight, or above. Until the present illness, the appetites of the children were good and they partook of everything that was on the family table. However, except in the cases of the first three patients whose diets were complete, as well as high in calories, the diets were seemingly characterized by an adequate supply of milk, a disproportionate and liberal supply of potato and bread and butter, and an insufficient amount of vegetables and fruits. In one case, a banana was taken, on the average, once daily and in another nothing more than 1 quart of milk was consumed. This patient, until two weeks before, had been receiving some breast milk and less cow's milk. Whether the breast milk and cow's milk were low in water soluble B vitamin it is impossible to state. The time of the year and the financial status of the mother both would make this seem possible.

One might conclude from these diets that the small proportion of vegetables and fruits was mainly responsible for any disturbance. The diets of the first three patients did include vegetables, which, however, may have been poor in the water soluble B vitamin. It may be that, contrary to our present ideas, the water soluble B content of raw food materials, such as potato, may lessen with age and under poor keeping conditions. It may be that it is not so much a more or less absolute deficiency in the diet of the water soluble B vitamin that is responsible for the development of herpetic stomatitis, as it is the intake of a diet that speeds up metabolism. The common occurrence of herpes labialis in women whose metabolism, as a result of pregnancy, lactation, menstruation and thyroid disease, is so much more frequently operated at a higher rate than is that of men, suggests such an interpretation, as does also the appearance of herpes labialis during the course of fevers. Such a condition of affairs might raise the requirement for the water soluble B. vitamin above the point of ordinary necessity, and so bring about a temporary water soluble B deficiency, which might instinctively be relieved by a reduction in the general food intake or by an increase in the consumption of water soluble B containing materials. It is well known that temporary starvation has a beneficial influence in rickets, tetany and diabetes. The self-imposed starvation that the patient with a severe herpetic and aphthous stomatitis undergoes may be the main reason for the more or less spontaneous recovery of these patients in one or two weeks, especially when starvation is carried out in conjunction with the use of local antiseptic washes. And the longer duration and increased severity of herpes zoster, if it be proved to belong to the same group of primary metabolic disorders, might be explained by the fact that, owing to the absence of painful lesions in the mouth, the food intake is liable to continue at a relatively high level.

It was pointed out above that not only herpetic and aphthous stomatitis, but acute gingivitis and ulcerative stomatitis likewise were remarkably improved by the administration of the water soluble B vitamin, and that Vincent's organisms were abundant in these cases. There seems to be little question that this group of organisms are factors in the development of ulcerative stomatitis, Vincent's angina and noma. Yet the students of these diseases are not satisfied as to the etiology. This is especially brought out by the data presented by Salle and Rosenberg[2] in a recent reconsideration of scurvy on the basis of new observations made during the war regarding the various types of stomatitis and gingivitis encountered in cases of scurvy. They quote Zlocisti,[2] as describing cases of scurvy in which the pathologic process in the mouth was, from the beginning, an ulcerogangrenous type ending, in some cases, in the development of noma. Aschoff,[2] while emphasizing the importance of the study of the relationship of scurvy and ulcerative stomatitis, asks the question, "Is the scorbutic affection of the mouth alimentary in nature or infectious, or both?" Salle and Rosenberg themselves encountered cases of scurvy showing ulcerative changes of the gums, which began as a delicate, yellowish white and became a smeary gray seam at the free border of the gums. Pure cultures of spirilla and fusiform bacilli were found in these cases. The ulcers appear early and sometimes are accompanied by the development of small and larger plaques on the labial and buccal mucous membrane—evidently cases of aphthous stomatitis. They conclude that this type of stomatitis is more amenable to arsphenamin therapy than to an antiscorbutic diet. Zlocisti also was able to produce a distinct improvement, in cases showing a severe ulcerative stomatitis and a beginning noma, by resorting to the intravenous injection of arsphenamin in huge doses. Morgan[3] has just reported that this type of stomatitis improves on intravenous arsphenamin administration, whereas the purely herpetic and aphthous types do not. He concludes that the latter lesions must have some other bacteriologic cause. Gerber[2] reports that spirilla and fusiform bacilli are to be found as harmless saprophytes in the mouths of normal people, especially under the gums. As a result of local injury or of a general debility, favorable conditions for the growth of these organisms is established and pathologic changes may be brought about. For a long time Heubner considered infantile scurvy a disease distinct from scurvy in adults because of the frequent presence of ulcerative gum lesions in adults, a condition not seen in infants. The net conclusion of Salle and Rosenberg is that, although the etiology of ulcerative stomatitis is still shrouded in darkness, it does not belong to the symptom group of scurvy.

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[2] Salle, V., and Rosenberg, M.: Ueber Skorbut, Ergebn. d. inn. Med. u. Kinderh. **19**:50-56, 1921.

[3] Morgan, E. A.: Ulcerative Stomatitis and Its Treatment by the Intravenous Injection of Arsenic, Am. J. Dis. Child. **25**:354 (May) 1923.

Arsphenamin unquestionably is effective in destroying Vincent's organisms. How, then, can we produce a similar result in our patients by a liberal administration of water soluble B? It is well known that antiseptics such as phenol and mercuric chlorid destroy bacteria. Likewise is it known that, in order to grow bacteria on mediums, certain food requirements must be met. Does not the arsphenamin therapy belong to the former class and may not the water soluble B therapy belong to the latter since it restores the tissues of the mouth to a normal state and so makes conditions unsuitable for the growth of these organisms? This seems to be the only conclusion that we can draw in these cases, and accordingly the changed state of nutrition of the tissues becomes the primary factor in the development of clinical conditions produced by the symbiosis of the spirilla and fusiform bacilli. It is, of course, probable that other parts of the human body are likewise changed and so may develop into satisfactory soils for other organisms as well. The disappearance of restless sleep and abdominal pain in our second patient is suggestive of this possibility. This theory would bring herpetic stomatitis and herpes labialis and their associated conditions into relationship with such disturbances as sprue,[4] and strengthens the impression that these infectious entities are basically metabolic and nutritional disorders. Pursuance of this theory may lead us to the source of various other metabolic disorders as well.

The improvement in our first cases on liberal quantities of orange juice, which evidently was due to its content of water soluble B vitamin, suggests that possibly some of the formes frustes of scurvy may be due to a water soluble B deficiency disturbance. Wiltshire,[5] for instance, reports the occurrence of hyperkeratosis of the hair follicles as scorbutic symptoms in Serbian soldiers, some of whom were among the finest specimens of physical manhood seen by him, and the majority of whom were above rather than below the average physical development. He comes to the conclusion that the cases were scorbutic because it seemed that nothing was lacking save the antiscorbutic vitamin. Heubner evidently was correct when he maintained that the scurvy of adults, because of its frequent association with ulcerations of the gums, was a different disease from the scurvy of infants. In all probability, the adults were suffering not only from scurvy but also from metabolic disturbance resulting from a water soluble B deficiency. Both conditions could be improved by the administration of orange juice, which supplies both the water soluble B and the water soluble C vitamins, the former, however, in smaller amounts. As a result, a severe form of ulcerative stomatitis occurring in a scorbutic patient might not improve so rapidly as would scurvy itself.

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[4] Funk, C.: The Vitamines, Baltimore, Williams & Wilkins, 1922, p. 369.

[5] Wiltshire, H.: Hyperkeratosis of the Hair Follicles in Scurvy, Lancet **2**:564 (Sept. 27) 1919.

It is clear that it is not safe to conclude that indefinite symptoms which disappear on the administration of orange juice are scorbutic in nature, unless no improvement in the symptoms has occurred after a previous liberal administration of the water soluble B vitamin in a form that is free from admixture with the water soluble C vitamin.

Assuming that the interpretations of our findings are correct, the more liberal, in fact, the daily use of such a dependable, economic water soluble B rich food as the canned tomato would seem to be rational.

CONCLUSIONS

1. The administration of the water soluble B vitamin produces in herpetic stomatitis, aphthous stomatitis, herpes labialis, acute gingivitis, and ulcerative stomatitis a remarkably rapid improvement and recovery.

2. The thirteen children and one adult in whom these conditions appeared, either singly or in combination, were well nourished and partook liberally of food until the stomatitis appeared.

3. In two cases, the relief by cathartic of a persistent constipation facilitated the therapeutic effect of the water soluble B vitamin.

4. From the observations in these cases, the other known vitamins, namely, the fat soluble A, the water soluble C and the fat soluble D, can be excluded etiologically.

5. It is suggested that the primary etiologic factor in these cases is metabolic and nutritional, and that any rôle that bacteria or similar agents may play in the further development of the local lesions are secondary.

6. This metabolic disturbance may be due to a disproportion between the water soluble B supply of the body and the metabolic requirements of the patient for this vitamin at a given time.

7. The presence in the individual of a metabolism that operates excessively or uneconomically, or both, because of hereditary or acquired physiologic or pathologic peculiarities or because of the consumption of a liberal and peculiar diet, or both, may be responsible for the metabolic disturbance, as suggested above.

8. Vincent's angina, noma and the various forms of herpes may belong to this class of disturbances.

9. Some of the formes frustes of scurvy may not be true cases of scurvy, but rather water soluble B disturbances that improve on the administration of orange juice because it contains the water soluble B vitamin, and it is suggested that in the future in such cases the water soluble B vitamin in pure form be administered liberally before orange juice is used.

10. The constant and liberal use of the canned tomato is advocated as an economic and dependable source of the water soluble B vitamin.

THE BLOOD SERUM CONTENT OF INORGANIC PHOSPHORUS AND CALCIUM IN PNEUMONIA *

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Peabody,[1] in 1913, found that adult patients with lobar pneumonia showed a markedly diminished excretion of calcium, sodium and chlorids, while the excretion of potassium and magnesium was normal throughout the disease. He also reported that the calcium and chlorids were present at a lower level in the blood stream during the febrile period, rising to normal a few days after the crisis. His findings in regard to the chlorids have been confirmed, but as regards the calcium, corroborative evidence is lacking. The method employed was probably not nearly so accurate as our present day methods.

We have been able to find only a few isolated determinations of the inorganic constituents of the blood in pneumonia. Kramer, Tisdall and Howland [2] report normal values for calcium in the serum. Denis and Talbot [3] found figures which range from 2 to 12 mg. per hundred cubic centimeters of plasma. Kramer and Tisdall [4] found the potassium increased in a few cases of pneumonia, as well as in certain other infections. These figures have recently been repudiated by Wilkins and Kramer,[5] who believe that the potassium content of the serum is normal in pneumonia. In a series of miscellaneous determinations by Kramer and Tisdall,[6] the sodium was found to be normal in the blood serum in one case of pneumonia.

We have not been able to find a single report of the inorganic phosphorus of the serum in this disease. It is this element rather than the calcium on which we intend to lay the emphasis in this article.

The stimulus for this investigation arose when we found the inorganic phosphorus content of the serum definitely reduced in an infant

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* Received for publication, Aug. 29, 1923.

* From the department of pediatrics of Lakeside Hospital and Western Reserve University, and from the Babies' Dispensary and Hospital.

1. Peabody, J.: J. Exper. Med. **17**:71, 1913.

2. Kramer, Benjamin; Tisdall, F. F., and Howland, John: Clinical Significance of Calcium Concentration in Serum of Children and Possible Errors in Its Determination, Am. J. Dis. Child. **22**: 560 (Dec.) 1921.

3. Denis, W., and Talbot, F. B.: Calcium in Blood of Children, Am. J. Dis. Child. **21**: 29 (Jan.) 1921.

4. Kramer, Benjamin, and Tisdall, F. F.: J. Biol. Chem. **46**:339 (April) 1921.

5. Wilkins, Lawson, and Kramer, Benjamin: Studies on the Potassium Content of Human Serum, Arch. Int. Med. **31**: 916 (June) 1923.

6. Kramer, Benjamin, and Tisdall, F. F.: J. Biol. Chem. **46**: 467 (May) 1921.

with bronchopneumonia, even though it had been on a highly antirachitic diet for the preceding six months. Ten days after the temperature had become normal, the inorganic phosphorus was also normal. Since then, we have made determinations on every pneumonia patient who has come to our wards, and in every instance the phosphorus has been distinctly below the normal value. One patient, whose record we located in searching for cases in the past, showed a normal phosphorus during the course of a lobar pneumonia, and his serum calcium was slightly reduced.

Many of the infants who come to the hospital with pneumonia are suffering from rickets also, and this disease, as we know, in many instances is characterized by a low inorganic phosphorus concentration in the serum. We have been able to collect a small number of patients who showed no clinical or roentgenologic signs of rickets. Two cases of known rickets have been included in this report because we believe that the pneumonic process can be shown to have had a definite influence on the phosphorus and possibly on the calcium of the serum.

The cases are reported in four groups.

A. PATIENTS WITH NORMAL INORGANIC PHOSPHORUS AND SLIGHTLY REDUCED CALCIUM CONTENT

Case 1.—A. D., aged 4 years, colored, entered the hospital on the fifth day of his illness, having a pneumonic consolidation of the right upper lobe. A blood test made on the second day in hospital revealed: calcium, 8.3; inorganic phosphorus, 5.4. The patient showed at this time a positive Chvostek's sign, and the electrical reaction gave a cathodal opening contraction of 5.5 milliamperes. He was given ultraviolet ray exposures, at first daily and later every other day. The fact that the roentgen ray revealed no evidence of rickets and that the Chvostek's sign was still present after sixty-two days of ultraviolet therapy led us to conclude that this was not a case of true infantile tetany. Because of the difficulty of obtaining blood, the next serum determination was not made until the sixteenth day in the hospital, and gave a calcium content of 9.1 mg. per 100 cubic centimeters. There was an insufficient amount for a phosphorus determination. Determinations carried out seven and nine weeks after admission gave: calcium, 10.1 and 10.5; phosphorus, 5.3 and 5.0.

B. PNEUMONIA IN OLDER CHILDREN

Case 2.—S. K., aged 6 years, white, whose condition was diagnosed lobar pneumonia, and whose previous diet was not known, while in the hospital was given S. M. A. (synthetic mild adapted), double strength, 180 c.c., four times a day, plus a soft diet for six days, and then "dubo" (whole milk plus 17 per cent. cane sugar), 180 c.c., four times a day, and the soft diet. Blood taken the day before the crisis showed calcium 8.6; phosphorus, 2.5; blood taken four days after showed phosphorus, 4.6.

Case 3.—S. Y., aged 9 years, white, whose condition was diagnosed lobar pneumonia (Chart 1) and whose diet was not known, in the hospital was given at first the regular soft diet and then the full house diet. Blood taken four days before the crisis showed calcium, 8.5, phosphorus, 2.5; one day after, calcium, 9.1, phosphorus, 3.4; five days after, calcium, 8.9, phosphorus, 4.5; nine days after, calcium, 9.5, phosphorus, 5.5.

Case 4.—L. H., aged 5 years, white, admitted to the City Hospital, suffering with bronchopneumonia, and whose previous diet was unknown, received the regular soft diet in the hospital. Blood taken during the course of the pneumonia showed phosphorus, 3.5.

C. INFANTS WITHOUT SIGNS OF RICKETS

Case 5.—W. M., aged 5 months, colored, whose condition was diagnosed bronchopneumonia, and who prior to entrance had been breast fed, in the hospital was given milk, 500 c.c.; oatmeal water, 500 c.c.; dextrimaltose, 40 gm.; 100 c.c., ten times a day. On account of positive diphtheria cultures, he was transferred to the contagious hospital before the second determination could be made. Blood taken two days before the temperature reached normal showed: calcium, 9.3; phosphorus, 3.0.

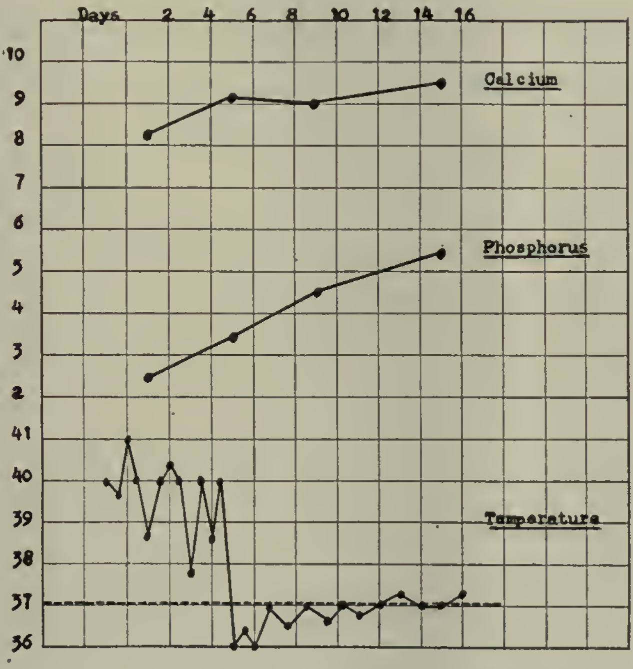

Chart 1 (Case 3).—Calcium and phosphorus determination (mg. per hundred cubic centimeters of serum), and temperature range (centigrade). Soft diet was given.

Case 6.—N. L., aged 11 months, colored, whose condition was diagnosed bronchopneumonia (Chart 2) and who had previously been fed on milk dilutions but had been given 1 teaspoonful of cod liver oil daily for the past two months, in the hospital was given whole lactic acid milk, 100 c.c., ten times a day, without cod liver oil. The temperature ranged between 39 and 41 C. (102.2 to 105.8 F.) for seven days. Then there were wide daily variations between

37 C. (98.6 F.) and 39 to 40 C. (102.2 to 104 F.). On the sixteenth day, the temperature was 40 C. (104 F.). Thereafter, it was normal. Blood taken the second day in the hospital showed: calcium, 10.1, phosphorus, 2.5; seventeenth day, calcium, 9.7, phosphorus, 5.0; twenty-third day, calcium, 10.6, phosphorus, 6.3; thirty-second day, calcium, 10.1, phosphorus, 5.4.

Case 7.—M. C., aged 10 months, white, who was suffering from bronchopneumonia and exudative diathesis, and who had been previously fed breast milk, in the hospital was given casein milk. Because the roentgenologic diagnosis was negative, we have placed this case in this class, although we believe that clinically this should have been considered to have a complicating mild rickets. The temperature was 40 C. (104 F.) for two days, and then fell abruptly to normal. Blood taken the third day in the hospital showed calcium, 8.0, phosphorus, 2.5; the seventh day, calcium, 7.9, phosphorus, 3.9.

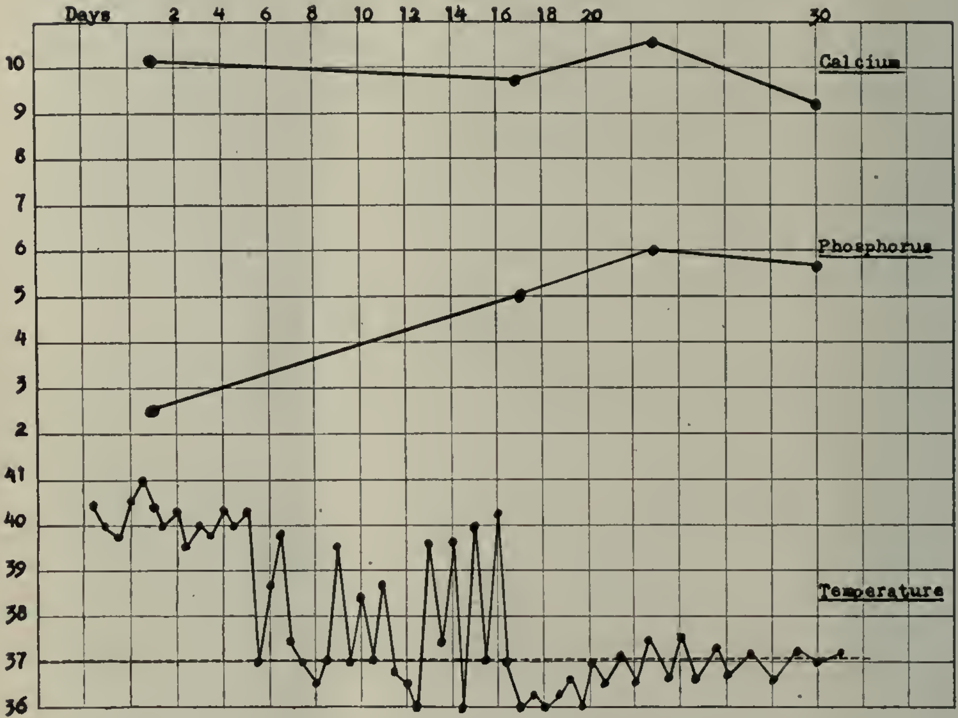

Chart 2 (Case 6).—Calcium and phosphorus determinations (mg. per hundred cubic centimeters of serum), and temperature range (centigrade). Whole lactic acid milk, 100 c.c. ten times a day, was fed.

Case 8.—W. H., aged 14 months, white, whose condition was diagnosed bronchopneumonia, had been fed on S. M. A. for the previous six months, and continued on this diet during her stay in the hospital. The temperature varied between 39 and 41 C. (102.2 to 105.8 F.) for eight days, and then fell gradually, reaching normal on the eleventh day. Blood taken the fifth day in hospital showed calcium, 9.3, phosphorus, 3.4; the twenty-first day, calcium, 9.9, phosphorus, 5.3; the sixty-fifth day, calcium, 10.2, phosphorus, 5.3.

Case 9.—W. R., aged 14 months, colored, whose condition was diagnosed bronchopneumonia (Chart 3) had been breast-fed, the feeding being complemented with S. M. A., until two months previous to admission. In the hospital, he was given two-thirds milk with dextrimaltose. The temperature was from 39 to 40 C. (102.2 to 104 F.) for six days, and then dropped by crisis. Blood taken the first day in hospital showed calcium, 10.0, phosphorus, 3.2; the eighth day, calcium, 10.2, phosphorus, 4.4; the eleventh day, calcium, 9.2, phosphorus, 5.7.

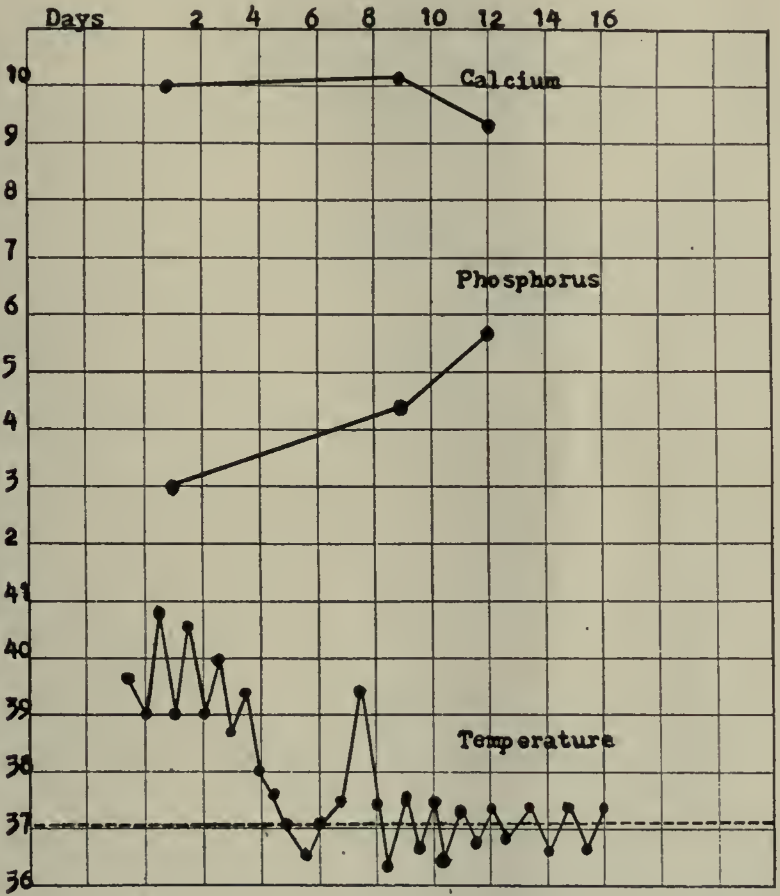

Chart 3 (Case 9).—Calcium and phosphorus determinations (mg. per hundred cubic centimeters of serum), and temperature range (centigrade). Whole milk, 660 c.c., oatmeal water, 340 c.c., and dextrimaltose, 70 gm., 200 c.c. five times a day, was fed.

Case 10.—M. B., aged 9 months, an Italian, who had bronchopneumonia, had been fed on certified milk dilutions, with 1 teaspoonful of cod liver oil daily for the past four months. She entered the hospital at the end of the disease. The feeding in the hospital was a two-thirds milk dilution for twenty-four days and then S. M. A. No additional cod liver oil was given. Blood taken one day after the temperature was normal showed calcium, 8.7, phosphorus, 2.6; twenty-four days after, calcium, 9.6, phosphorus, 4.6; forty-seven days after, calcium, 11.1, phosphorus, 7.6.

D. INFANTS WITH RICKETS BUT APPARENTLY SHOWING THE INFLUENCE OF THE PNEUMONIA

Case 11.—B. S., aged 20 months, colored (Chart 4), had been in the hospital for nearly a year following a double mastoid infection. Under antirachitic therapy he had persistently shown a low calcium content of the serum and positive clinical and roentgenologic signs of rickets. On repeated examinations, the inorganic phosphorus had been above 5 mg. per hundred cubic centimeters over a period of eight months. Electrical reactions never showed a cathodal opening contraction of less than 5 milliamperes nor an anodal reversal after the antirachitic food was given. The fourth day after the onset of a severe bronchopneumonia, the calcium was 8.0 and the phosphorus 2.5 mg. per hundred cubic centimeters of serum. Five days later, he was given disodium phosphate, 5 grains every two hours. A blood specimen obtained twenty-four hours after this and a few hours before death gave a calcium value of 5.5 mg. and a phosphorus of 5.0 mg. At necropsy, besides the pneumonia, a chronic nephritis was found.

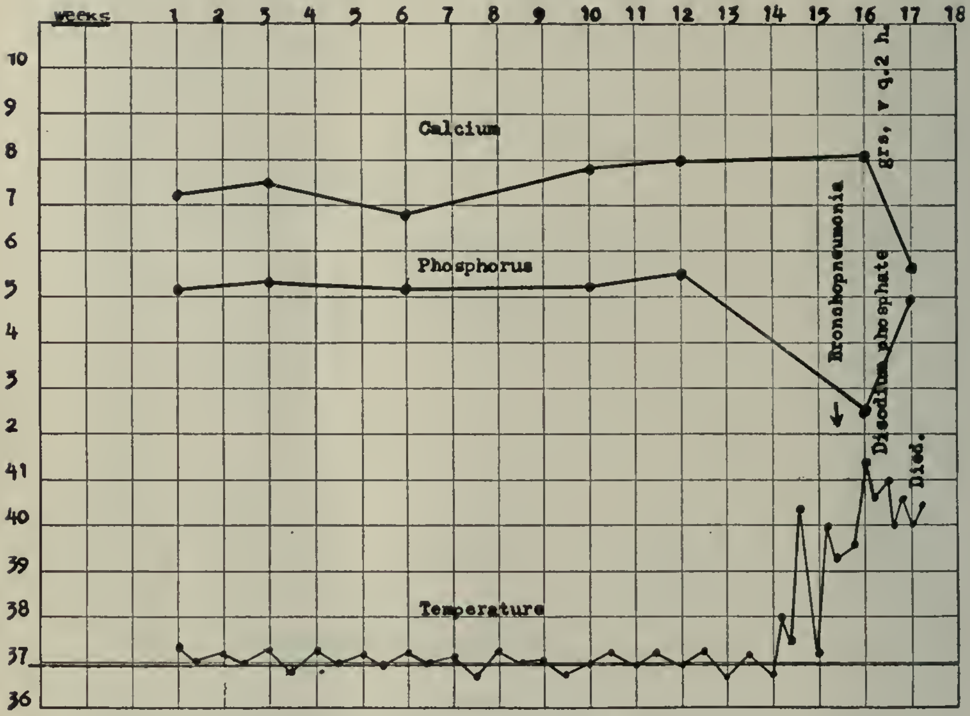

Chart 4 (Case 10).—Calcium and phosphorus determinations (mg. per hundred cubic centimeters of serum), and temperature range (centigrade). S. M. A. (synthetic milk adapted), double strength, 150 c.c., five times a day, and farina and vegetables were fed.

Case 12.—M. L., aged 6 months, colored, whose condition on admission was diagnosed rickets and tetany, showed a calcium of 6.6 and a phosphorus of 4.5 mg. per hundred cubic centimeters of serum. After he had been fed on S. M. A.

for two weeks, his calcium content was 8.2 and phosphorus, 4.4. Four days later, pneumonia developed. On the seventh day of the pneumonia, the calcium was 7.2 and the phosphorus 2.6. On the twenty-second day of the pneumonia, the results were: calcium, 8.8, phosphorus, 2.4. A low fat lactic acid milk had been substituted for S. M. A. on the seventeenth day of the pneumonia.

In addition to these cases, we have determined the phosphorus in twelve cases of adults with lobar pneumonia. We have not been able to determine the calcium on all of these.[7] We were not always able to bring these specimens of blood to the laboratory on the same day they were withdrawn, and although they were kept in the refrigerator, sometimes there might have been an opportunity for the inorganic phosphorus to increase before the determination. The results are given in the accompanying table.

Results of Calcium and Phosphorus Determinations in Twelve Adult Cases

	Calcium Mg.	Phosphorus Mg.
	9.8	3.1
	10.1	1.5
	8.8	2.3
	8.9	3.0
	10.4	2.3
	....	1.8
	....	3.4
	....	2.8
	....	3.4
	....	2.2
	....	3.5
	....	3.5
Average	9.6	2.7

COMMENT

In nine of ten nonrachitic children with pneumonia, the inorganic phosphorus of the serum has been found decidedly reduced. The calcium has been slightly reduced in some and normal in others. In two cases of "low calcium rickets," in which determinations had been performed before the onset of the pneumonia, the phosphorus dropped with the onset of the pneumonia. In seven of the cases, determinations were made during convalescence, and in every instance the phosphorus had increased to a normal or nearly normal value. In only two of the cases was there anything administered which might have been considered as having any antirachitic effect. One of these was in a child of 6 years who could scarcely have had the rickets, and the other was in an infant who had been receiving the same diet for six months previous to the onset of the disease. The calcium in every instance but one was normal during convalescence in those cases in which it was determined.

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[7] We are indebted to the medical resident at the Cleveland City Hospital, Dr. C. P. Huston, for his cooperation in obtaining the specimens of blood for us.

The average findings for the adult cases were practically the same as have been considered normal by investigators of this subject. We should prefer, however, not to draw any conclusions from these results on account of the conditions mentioned above.

With the scant data presented here and such as we have been able to find in the literature, we do not feel justified in attempting to offer a theory in explanation of these results. They suggest the causation of rickets by pneumonic and possibly other infections. With our present knowledge of the level of chlorids and the bicarbonates in the blood in pneumonia, and with the work of Lord[8] on the acidity of the pneumonic exudate, this data would seem to make the study of the acid-base equilibrium in this disease an interesting subject for further investigation.

CONCLUSIONS

1. In nine of ten cases of pneumonia in nonrachitic children, the inorganic phosphorus of the serum was decidedly reduced during the febrile stage and rose to normal during convalescence.

2. The calcium was slightly reduced in some of the cases and normal in others. In those cases in which it was reduced, it rose to normal during convalescence, except in one instance.

3. These findings may offer an explanation of the rôle played by respiratory infections in the development of rickets.

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[8] Lord, F. T.: Relation of Pneumococcus to Production of Acid in Fluid Culture Mediums and Reaction of Pneumonic Lung, J. A. M. A. **72:** 1364 (May 10) 1919; Factors Influencing Recovery and Resolution in Lobar Pneumonia, ibid. **73:** 1420 (Nov. 8) 1919.

A COMPARISON OF THE VALUE OF MILK AND ORANGES AS SUPPLEMENTARY LUNCH FOR UNDERWEIGHT CHILDREN*

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The study of nutrition, as applied to the school child, has at the present time a well defined place in the school program. Physical fitness is an unparalleled asset to the adult. That some at least of the disability found in the adult may be laid to defective nutrition during childhood was probably first indicated by investigations in England following the Boer War, when two thirds of the recruits were rejected because of physical inperfections.

Emerson[1] states: "There is no evidence in the weighing and measuring of children that malnutrition, if left untreated, tends on the whole to correct itself. The percentage of malnutrition for older children is no less than that for younger children. It is, then, fair to assume that the nation's list of physically unfit is supplied by this group of malnourished children in the schools."

The conclusion has thus been reached that rational feeding in infancy and childhood has a vital relationship to the development of physical strength and of resistance to infection. As a result of these findings, feeding has been introduced into the schools. A wave of nutrition reform has swept the country. Studies have been made concerning causes and results of malnutrition; statistics have been gathered; preventive measures formulated, and varied attempts made to overcome this insidious condition.

"A scale in every school" and "a quart of milk a day for the growing child" are nationwide slogans. One of the most common methods of overcoming undernutrition among school children is the introduction of a supplementary lunch, consisting usually of milk and crackers.

The value of milk in the diet is unquestioned. McCollum[2] in his studies on animals has found that diets which were derived from miscellaneous sources, such as cereal grains, legumes, tubers, fleshy roots, with or without meats but supplemented with liberal amounts of milk, sufficed to maintain satisfactory growth and vigor. Sherman and Hawley[3] have recommended a diet containing a quart of milk a

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* Received for publication, July 19, 1923.

* From the Laboratory of Household Science, University of California.

[1] Emerson, W. R. P.: Nutrition Clinic in Public School, Am. J. Dis. Child. **17**:251 (April) 1919.

[2] McCollum, E. V.: The Newer Knowledge of Nutrition, New York, The Macmillan Company, 1922, p. 403.

[3] Sherman, H. C., and Hawley, E.: J. Biol. Chem. **53**:375 (Aug.) 1922.

day and a normal allowance of other foods. This will furnish a gram of calcium a day for the growing child, the amount which they have found necessary to induce optimum storage of calcium. Because of these and like statements, milk has had an unrivaled place as a school lunch. Thousands of children are receiving it at schools in this and other countries. The result has been in most cases a gain in weight for such children over the average. Palmer,[4] of the Detroit Department of Health, conducted in 1919 an experiment to determine comparative gains of children receiving a school lunch and those having no supplementary feeding. At the end of eleven weeks, the children in the former group averaged a gain of 25 ounces above that expected; those in the latter (control) group, a 1 ounce loss. Many similar but unpublished tests have been carried on, demonstrating to a large extent the efficacy of milk for the underweight child.

However, it has been forcefully demonstrated by many investigators that all milk is not of equal food value since its vitamin content is altered by the fodder of the cow and also by the application of heat. Hess,[5] while he advises the use of milk because of the security it provides against infection, states that it is an incomplete food, and a contributing cause of infantile scurvy if it is pasteurized or if fed after ageing. That the calcium content of milk is altered by heating has been shown by Daniels and Stuessy,[6] who demonstrated that rats fed on milk boiled for one minute failed to grow normally unless the calcium deposit, produced by boiling, was combined with the milk. Pasteurization of milk causes a similar precipitation of the calcium salts.

Another point to be considered when milk is to be fed as a midmorning lunch is its satiating effect. In many instances, a glass of milk taken between meals or at the beginning of the meal will cause lack of appetite; and, as the undernourished child already has a tendency to diminish his food intake, this may be a more serious consideration than it appears on the surface.

Oranges also are a protective food and have an important place in the diet. Their potency as a source of fat-soluble A, water-soluble B and water-soluble C has been proved by many experiments on animals. Morgan[7] has shown that orange juice, orange oil and orange peel are valuable sources of the fat-soluble vitamin. The experiments of Osborne and Mendel[8] indicate that, volume for volume, orange juice is as rich as milk in water-soluble B and somewhat less rich in vitamin A. According to Givens and McGluggage,[9] orange juice is much richer than milk in the antiscorbutic vitamin. The vitamin in orange is, in contrast with most other antiscorbutic food, comparatively stable to heat and oxidation. Experimental work on the values of orange juice in infant feeding goes to prove that it is important not only as a source of the antiscorbutic vitamin, but also as a stimulant of appetite. Babies not gaining normally on the ordinary amount of orange juice (15 c.c., as fed by Daniels) receive a marked stimulation to growth when 45 c.c. is administered.[10] Newell and Miller[11] have recently demonstrated that orange juice added to the diet of underweight children causes gain in weight. "The percentage of expected gain of the group was changed from 49 for the four months preceding the experiment to 132 for the three months during which orange juice was given."

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[4] Palmer, G. T.: Am. J. Pub. Health **12**:134 (Feb.) 1922.

[5] Hess, A. F.: Infantile Scurvy, Am. J. Dis. Child. **12**:152 (Aug.) 1916.

[6] Daniels, A. L., and Stuessy, S.: Boiled Milk, Am. J. Dis. Child. **11**:45 (Jan.) 1916.

[7] Morgan, A. F.: Am. J. Physiol. **64**:522 (May) 1923.

[8] Osborne, T. B., and Mendel, L. B.: Proc. Soc. Exper. Biol. & Med. **19**: 187, 1922.

In order to determine the state of nutrition of a child, a statistical standard of some sort is necessary. Such a standard, determined by averaging the growth of thousands of children selected, for the most part, at random, is vitiated in that it includes a large number of malnourished children whose measurements lower the average of height and weight. While a growth standard is essential for the study of the health of a child, it must also be remembered that each child is an individual and will grow at his own rate. Porter,[12] in a recent study of the relative growth of Boston school boys, has undertaken to determine the growth of the individual as compared with the average. He gives the limits within which statistical growth standards may be used in relation to the individual. However, as Affleck[13] concludes, "It is believed that in the case of normal development each child would not differ widely from the corresponding figures in the standard."

In ascertaining the state of well being of the child, environment and social standing as well as the physical condition of the body are to be considered. An unfavorable environment usually parallels lack of medical care, the two resulting in a failure to gain in weight and stature. The most common physical defects causing undergrowth and poor nutrition are carious and infected teeth, and enlarged and infected tonsils and adenoids. While these conditions do not necessarily impair nutrition, the marked improvement after the defects have been remedied demonstrates the fact that they are undoubtedly a factor in malnutrition.

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[9] Givens, M. H., and McCluggage, H. B.: Orange Juice in Scurvy, Am. J. Dis. Child. **18**:30 (July) 1919.

[10] Byfield, Amy H.; Daniels, Amy L., and Loughlin, Rosemary: Antineuritic and Growth Stimulating Properties of Orange Juice, Am. J. Dis. Child. **19**:49 (May) 1920.

[11] Newell, F., and Miller, E. W.: J. Home Econ. **15**:241, 1923.

[12] Porter, W. T.: Am. J. Physiol. **61**:311 (July) 1922.

[13] Affleck, G. B.: Pediat. Sem. **27**:324, 1920.

These puzzling and difficult considerations of growth standards, physical defects and variations in home diet and in heredity of the underweight children studied were kept well in mind when the experiment here described was undertaken. It seemed worth while to make as accurate record as possible of the relative growth shown by groups of children similar in economic and physical status who differed only in the character of supplementary lunch provided at school.

The Claremont School, Oakland, Calif., was chosen for the test. Since most of the children attending this school came from middle class homes, the economic factor was eliminated to a great degree. Thirty-three per cent. of the children in the school were found to be 7 per cent. or more under weight when judged by the Wood scale.[14] This scale was chosen as typical, and as perhaps the most used of all tables at present available. The sources used for this table, as revised in 1920, which included at least 250,000 of each sex, were: statistics of American children published by Baldwin, Boas, Bowditch, Hastings, Holt, Porter and others; statistics from about 10,000 records of children in the Horace Mann School, collected for eighteen years; statistics of life insurance companies for periods of fifteen years and upward, and Dublin's statistics of children from 14 to 16 years of age examined in New York State for the issuance of working papers. These tables are printed on a 4 by 5 card by the Division of School Hygiene, Bureau of Education, Department of the Interior, Washington, D. C. Net heights are given, but weights are taken with average indoor clothing.

While it is realized that the factor of seasonal variation might influence to a marked extent the monthly growth of the child, some standard had to be set whereby a comparison of such fractions of growth could be made. For this purpose the table prepared by Holt [15] was used. As the object in view was a comparison involving food, and not seasonal growth, the data obtained from this source were deemed adequate.

DATA SECURED CONCERNING CHILDREN

Age, sitting height, standing height and weight of each child were determined according to directions from the United States Public Health Service. Age was recorded to the nearest birthday. Sitting height was recorded as follows at the beginning of each experimental period; the child was seated on the floor with the back against the measuring tape, his knuckles on the floor, fingers pointing back, knees flexed. Each child was told to sit straight and make himself as tall as he could. Standing height without shoes was taken to the nearest quarter of an inch at the beginning and end of each test period. The child stood on a level surface, heels, buttocks, shoulders, and head lightly touching the wall, on which was a measuring tape, and with eyes straight to the front and arms hanging at the sides. Weighings were made weekly, at approximately the same hour of the day, weight being taken to the nearest quarter of a pound, with shoes and sweaters or coats removed. A Fairbanks scale was used. Throughout the experiment, variations in weight and not in height were considered; for, as a sensitive indication of the influence of diet on health, the measure of weight is ordinarily considered more reliable than that of stature.

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[14] Wood, T. D.: U. S. Dept. of Interior, Bureau of Education, March, 1920.

[15] Holt, L. E.: Public Health (Michigan) **10**:588, 1922.

Dental and physical examinations of all the children in the test groups were made. In the former, special attention was given to soundness and regularity of the teeth, cleanliness and state of the gums. The physical examination included nose, throat and neck, chest, heart and lungs. In any case of doubt as to bodily fitness, the child was eliminated from the final calculations; thus each child in the experiment was considered free to gain.

TABLE 1.—*Supplementary Lunch Schedule*

Lunch Fed and Amount Given Each Day	Winter Term (8 Weeks)			Spring Term (8 Weeks)		
	Number of Children in Group	Actual Cost to Child Each Week, Cents	Estimated Average Cost to Child Each Week, Cents	Number of Children in Group	Actual Cost to Child Each Week, Cents	Estimated Average Cost to Child Each Week, Cents
Milk, ½ pint; 2 graham crackers	28	25	25	37	25	25
Orange, 1 of medium size; 2 graham crackers	10	25	25 to 30	38	0	20 to 25
Milk, ½ pint; orange, 1 of medium size; 2 graham crackers	26	25	45	..	..	..
Orangeade, ¼ pint; 2 graham crackers*	11	..	20 to 25	30	5	20 to 25
Control	34	..	..	35	..	..

* None in winter term.

GROUP DIVISION OF THE CHILDREN

After the identity of the children who were 7 per cent. or more underweight had been determined, this group was assembled and the purpose of the test explained to them. Thus, voluntary cooperation was obtained, and each child chose, so far as possible, the type of lunch he wished. Table 1 gives information concerning the lunches fed, the number in each group and the cost, actual and estimated as average, of each lunch.

Detailed Information Regarding Lunches (Table 1).—Pasteurized milk, which had during the past year been sold to the children, was continued as usual. Two large graham crackers were supplied with each feeding. Oranges were furnished on the same basis as the milk during the first feeding period. Because of the irregularity with which the children bought the orange tickets, the number diminishing from twenty-seven in October to ten in December, arrangements were made with the California Fruit Growers Exchange whereby oranges were given free to the children for the second test period. A ticket, sold at the beginning of the term for 40 cents, paid for the graham crackers for eight weeks. The milk and orange group was not continued during the second term because (1) no striking results were obtained during the experimental period, and (2) it was considered wise to increase the number of children in the more essential groups. The feeding of orangeade during the winter period was added when the Household Science Department of the University of California was given several cases of concentrated orange juice. It was given to the children free of charge and without the addition of graham crackers. For this reason, the figures obtained were not on a par with those of the other groups. Therefore, for the spring test period, tickets were sold on the same basis as for the oranges.[16] From the point of view of both heating and oxidation, the juice should be vitamin rich. A 4-ounce bottle contained the equivalent of twelve large oranges. In order that each child might receive daily the juice of one orange, each bottle was diluted with twelve parts of water. To mask the flavor of the oil, 2 tablespoons of sugar was added for each bottle used. The control group consisted largely of children whose parents disapproved of a midmorning lunch. They were measured, weighed and examined as were the other children, except that, during the last test period, less frequent weighings were taken. This was done to withhold from the child knowledge of gain or loss in weight which might alter his course of action as regards food intake. Careful account was taken of all children who, during the eight weeks' period, changed in any way the school lunch. Records of these children were eliminated in final calculations.

Method of Feeding Lunches.—The lunch was administered during two eight-week periods, October 23-December 15, and January 8-March 2. The feeding was done on school days only, and at the forenoon recess. No attempt was made to check on or alter the home diet. Near the end of each of the test periods, a questionnaire was sent home, regarding the amount of milk and oranges taken each day at home, and how this amount had been influenced by the feeding of a lunch at school. The main object of the questionnaire was to ascertain whether, because of the school feeding, additional milk or orange was being consumed at home. This was sometimes found to be the case, especially with the control group. All such children were eliminated from the final records. By means of the questionnaire, data were obtained also concerning the adequacy of the home diet and the effect of the school feeding on the appetite and on the health of the child.

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[16] The manufacturer's description of the method used in concentration is as follows: The oranges are thoroughly washed and crushed, and the juice is concentrated under pressure. During the greater part of the time, the juice is at about 90 F., for only a fraction of a minute reaching a temperature of over 110 F. Only twenty minutes elapse from the time the juice is in the orange until it is in the sealed bottle.

Data and Comment.—At the end of each feeding period, the data at hand were checked, there being used in final calculations the records of children who (1) were free to gain as determined by dental and physical examinations and by frequent observations as to condition of health; (2) had continued to eat the school lunch throughout the eight weeks, and (3) had not been influenced, as far as could be determined, by change of home diet. The observed gain per week of each group was determined and compared with the gain expected according to the Holt table for monthly gain in weight.

TABLE 2.—*Comparative Gain on Supplementary Lunches*

Lunch Taken	Winter (8 Weeks)			Spring (8 Weeks)		
	Expected Gain for Each Child, Kg.	Observed Gain for Each Child, Kg.	Percentage of Gain for Each Child Above That Expected	Expected Gain for Each Child, Kg.	Observed Gain for Each Child, Kg.	Percentage of Gain for Each Child Above That Expected
Orange...............	0.579	1.397	141.27	0.529	1.152	117.76
Orangeade...........	0.599	1.122	87.31	0.534	0.945	76.96
Milk.................	0.458	0.945	106.33	0.509	0.911	78.97
Milk and orange.....	0.481	1.066	121.62	.....	.....	......
Nothing..............	0.537	0.690	28.49	0.544	0.589	8.27

GAIN IN WEIGHT AS INFLUENCED BY DIFFERENT TYPES OF LUNCHES

Charts 1 and 2 and Table 2 show winter and spring gain for each group. It will be noted that the control group during both terms gained slightly in excess of the expected gain as determined by the Holt table. As these children were in every respect normal and as their environment was similar to that of the other children taking part in the experiment, this group might consistently be considered as making the expected gain, and comparison of gains in the other groups be made in every case with the control group. In Table 2, comparison has been made using Holt's figures for expected increase in weight.

A gain in excess of that expected was noted in each supplementary lunch group. The increase is so nearly constant and so large in proportion to what is considered average that it may be considered proof of the value of the midmorning lunch. The fact that a large number of these children come from homes which can supply all dietary needs also tends to establish this point. Aside from a gain in weight, an improved condition of well-being is evident on the part of many of the children. This is shown by actual observation of the children, remarks from parents and data from the questionnaires. Despite the fact that the numbers of children in the winter orange and orangeade groups were extremely small, the gain for each child is comparable to that in the spring groups, in which there were more children.

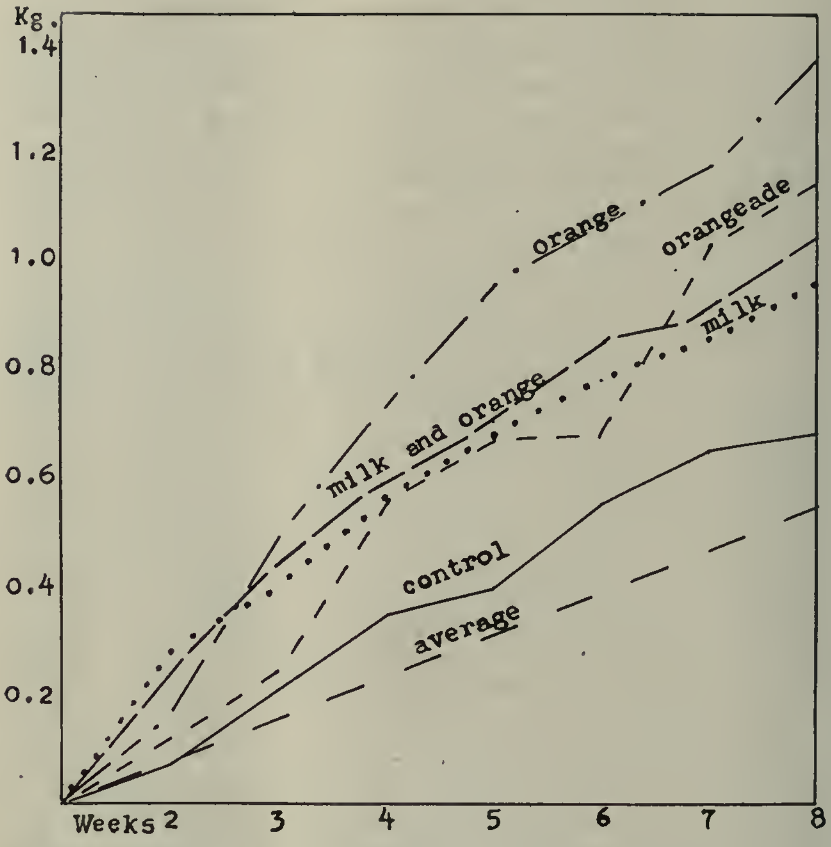

Chart 1.—Observed gain for each child in different groups during supplementary lunch feeding (winter).

A comparison of the gains of the orange and milk groups is of interest. Oranges apparently are superior to milk as fed to the children involved in the test. As determined by the questionnaire, most of the children were receiving sufficient milk at home. On the other hand, oranges were used less plentifully; in many cases not at all. Therefore, the oranges fed at school supplemented the milk and caused more rapid gain. Milk has long been adopted as the best food for the supplementary lunch. The fact that another food may be used in place of milk may be welcomed by many whose children do not take milk because of an aversion to it, or who object to the school lunch because of its depressing effect on the consumption of food at home. The orange lunch instead of decreasing total food intake is likely to increase it, owing to the water-soluble vitamin in the orange. Another point in favor of the oranges is the ease with which they may be handled, since no preparation is necessary before they are sold. Further investigation, using a group of children from a poor district, may show decidedly different results and will make an interesting study. The natural likes and dislikes of the individual child must be considered, as well as the home conditions.

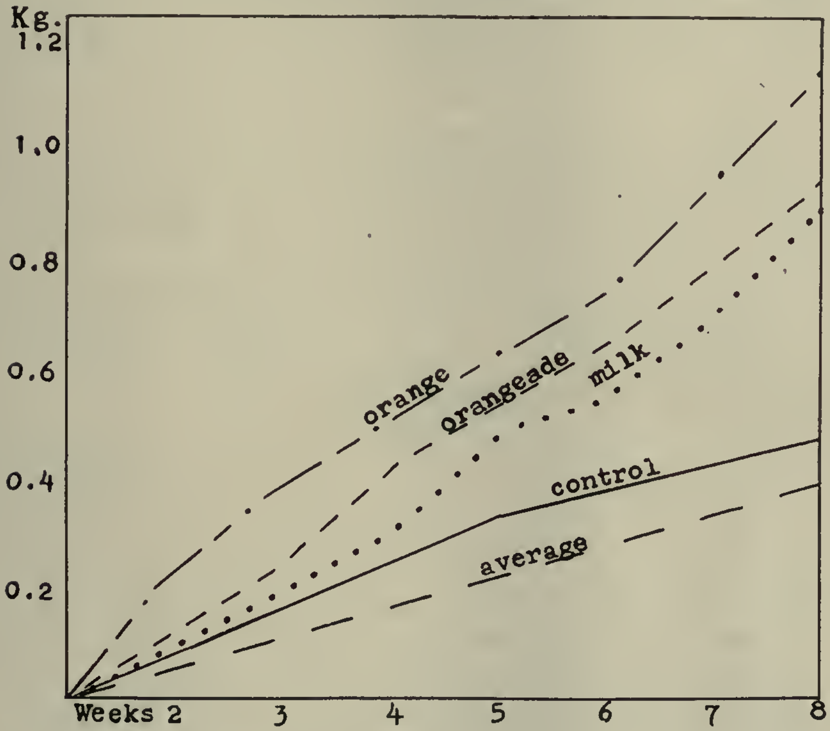

Chart 2.—Observed gain for each child in different groups during supplementary lunch feeding (spring).

The good gain of the orangeade group shows the efficacy of bottled orange juice. While it did not prove so satisfactory for gain in weight of the underweight child as did the fresh orange, it may be considered as having an important place in child feeding, especially where oranges are not available or, for other reasons, their use is not justified. An interesting deduction may be made from the comparative winter and spring gain of the orangeade group. Despite the fact that the lunch of this group in the winter did not contain graham crackers, the gain per child was equivalent to that of the spring group. This indicates, as does the comparative gain of the orange group over the milk group, that it is not calories that are lacking in the diet of these children.

Milk and oranges taken at the same time appear to stimulate growth at a level slightly higher than milk or orangeade alone, but not so much as do oranges. The reason for this is not apparent, and the subject will necessitate further investigation. As its bearing on the experiment was a minor one, the group was dropped during the spring term.

COMPARISON OF THE WOOD AND PIRQUET STANDARDS FOR GROWTH

Among many other indices for growth which have been formulated by statisticians is the pelidisi introduced by Pirquet of Vienna.[17] He believes that the sitting height is more accurate than standing height as the means for estimating the state of nutrition. The formula for the pelidisi is $\sqrt[3]{\frac{10 \times \text{weight in grams}}{\text{sitting height in centimeters}}}$; in muscular adults and plump infants, 100 is the average; in children, 94. A table has been prepared by Carter [18] which simplifies the calculations.

TABLE 3.—*Comparison of Percentage Under Weight According to Wood Scale with Pelidisi*

Percentage Under Weight	Number of Children	Pelidisi Average	Number of Children with Pelidisi Over 94	Number of Children with Pelidisi Under 94
7	30	94.6	19	11
8	34	94.7	25	9
9	28	94.5	19	9
10	27	93.6	15	12
11	29	93.6	15	14
12	18	93.0	5	13
13	11	93.6	5	6
14	14	92.9	6	8
15	13	93.9	7	6
16	22	93.0	9	13
17	8	93.1	4	4

The use of the Pirquet scale in the determination of nutrition of American children has been discussed in detail, and its applicability questioned. Table 3 gives a comparison of the percentage under weight of the children observed in this study according to the Wood and to the Pirquet scale. A great variation among individual children is shown. Many children who are decidedly underweight have a high pelidisi; yet casual observation shows them to be in a poor state of nutrition.

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[17] Pirquet, C.: Ztschr. f. Kinderh. **6**:256, 1913.

[18] Carter, W. E.: Pirquet System of Nutrition and Its Applicability to American Conditions, J. A. M. A. **77**:1541 (Nov. 12) 1921.

PHYSICAL DEFECTS AS RELATED TO MALNUTRITION

In Table 4, the physical condition of the underweight children studied may be noted. These children are all 7 per cent. or more underweight, but only those with minor defects have been used in the calculations. A large percentage of the children had only minor defects. This fact was commented on by examiners, who found the children remarkably free from conditions which would hinder normal growth. A small percentage of chest, heart and lung defects were found as compared with defects of teeth, throat and nose. Many of the children with rather serious defects have gained remarkably, thus showing that, while physical disabilities are an influencing factor in nutrition, they do not always retard growth.

SEASONAL VARIATION IN GROWTH

A periodic acceleration and retardation in the growth of children has been recognized for many years. The maximal period for growth seems to be during the summer and fall months, and according to various authorities is due not to a dietetic change but to atmospheric temperature and life in the open. Faber,[19] in observing the growth of infants in San Francisco, obtained a slight seasonal variation in growth, as might be expected in that climate, which shows small temperature variation, with relatively cool summers. On comparing the seasonal growth of the children involved in the present investigation; that is, of children who had the same type of lunch throughout the entire experiment, a slight seasonal variation was noted. The average gain for these children from October to December was 0.73 kg., as compared with a 0.56 kg. gain from January to March. It may also be noted from Table 2 that the observed gain for each child

TABLE 4.—*School Ranking as to Physical Defects*

Defect	Number of Children Ranked as			Percentage of Children Ranked as		
	Condition Good	Condition Fair, Defect Not Serious	Needing Attention	Condition Good	Condition Fair, Defect Not Serious	Needing Attention
Nose	191	83*	0	70	30	0
Teeth, cleanliness	133	140	11	47	49	4
Teeth, regularity	195	70	19	69	25	6
Teeth, soundness	180	97	7	63	35	2
Throat	205	63	8	74	23	3
Neck	219	57	0	79	21	0
Chest	130	38	1	76	23	1
Heart	138	14	3	89	9	2
Lungs	132	21	1	86	13	1

* Large number due to colds which were present at time of winter examination.

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[19] Faber, H. K.: Arch. Pediat. **37**:244 (April) 1920.

during the winter period was greater in every case than was the gain in the spring. These figures appear to signify that the winter months were more favorable for gain in weight than was the spring period.

SUMMARY

A comparison of growth variation in underweight children as influenced by different types of supplementary lunches has been made. The children were free to gain, as far as could be determined by physical and dental examination. The economic status of the majority of the homes permitted provision of adequate food. The results seem to demonstrate that:

1. A midmorning lunch is of value in overcoming a condition of underweight in children.

2. Oranges, as fed to the children in this investigation, seem most efficacious in producing a gain in weight. This may be due to the vitamin content of the orange.

3. Milk, while it produces a favorable increase in weight, is not the only food valuable for the midmorning lunch. The less marked gain in weight which milk produced in this test may be due to its lack of the antiscorbutic vitamin and to its retarding effect on the appetite.

4. Concentrated bottled orange juice appears to be of marked value in stimulating growth in the underweight child. While it has not proved equal to fresh oranges, it is quite effective, and may, if the fresh fruit is not available, supply the vitamins necessary for growth.

5. A comparison of the Pirquet with the Wood standard of nutrition indicates the probable inapplicability of the former for American children.

6. A possibility of seasonal variation for California children is manifest.

The need for further experimentation is keenly felt. A detailed study of home diet in relation to school feeding should throw more light on the subject; also, a repetition of this work under the same or slightly varied conditions, either in the home or at school, will help to prove or disprove observations made here. Larger numbers of children, more closely controlled conditions, longer periods of feeding, would give more reliable results. It is with a desire to arouse more interest in a subject of such vital importance, to stimulate more experimentation along this and related lines, that these results are offered.

OBSERVATIONS ON THE EFFECT OF COMPLEMENTAL FEEDING IN NEW-BORN INFANTS *

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The literature is filled with many theories and facts regarding the loss of weight in new-born infants during the first few days of life. The ultimate summary of both theories and facts seems to resolve itself into the practical fundamental we daily observe; namely, that the output over this period is greater than the intake. Bailey and Murlin[1] demonstrate, however, that, in addition, there is a combustion of carbohydrates and fats during this period. They show from their studies of new-born infants that the respiratory quotient rises as high as 1.0 on the first day of life, which indicates the combustion of carbohydrates. Thereafter, it drops to 0.67 on the second day, and remains in the neighborhood of 0.70 for the full two days, indicating a condition of starvation and the combustion of fat.

Invariably, the statement brought forth by these clinical and scientific observations is that this is a physiologic process, and consequently should be recognized, and no interference with nature should be made. Together with this, the arguments are advanced that the intestinal tract is still immature; that the normal intestinal flora, as indicated by Czerny,[2] is disturbed if other foods are offered before the advent of the mother's milk, and that such interference produces later intestinal disturbances. These arguments, though impressive on paper, are not always clinically sound, and I feel there is sufficient evidence to refute them.

In the first place, any condition of immaturity of the intestinal canal which exists at birth cannot undergo any marked degree of change over the period of the first few days. Among animals, as Kehrer[3] has observed, nursing takes place immediately from fairly full udders, and, consequently, a relatively smaller loss of weight is experienced. Also, Adair and Steward[4] show definitely that even

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* Received for publication, July 19, 1923.

* Investigation conducted at St. Luke's Hospital, Chicago.

* Read before the Chicago Pediatric Society, April 17, 1923.

[1] Bailey, H. C., and Murlin, J. R.: Energy Requirements of the New-Born, Proc. Soc. Exper. Biol. & Med. **9**:109, 1914. The Nutrition of the New-Born, editorial, J. A. M. A. **63**:404 (Aug. 1) 1914.

[2] Czerny, A., and Keller, A.: Des Kindes Ernährung, Ernährungsstörung und Ernährungstherapie, Leipsig und Wien, F. Deuticke **1**:36, 1906.

[3] Kehrer, F. A.: Ueber die Ursachen der Gewichtsver-änderungen Neugeborener, Arch. f. Gynäk. **1**:124, 1870.

[4] Adair, F. L., and Steward, C. A.: Milk Ingestion in Relation to Changes in Body Weight of New-Born Infants, J. A. M. A. **78**:1865 (June 17) 1922.

though infants of multiparas have higher average birth weights, they lose less because, as they have demonstrated, the mother's milk appears earlier and is more abundant. Finally, none of us hesitate to institute additional and early feeding to premature and other underweight new-born infants. Clinically, in these cases, we have noted no evidence of an immaturity of the intestinal tract; nor have we experienced any evil results from a theoretically abnormal intestinal flora.

That an infant actually needs food over this period is further indicated by Bailey and Murlin,[1] who, from the figures noted above, calculate that the food requirement during the first four days of life for a large infant weighing 4.5 kg. is 1.7 calories per kilogram for each hour, and for the small infant of 3.0 kg. as 2.0 calories per kilogram for each hour. These authors assert that the colostrum furnishes 65 calories per hundred cubic centimeters. When we find, however, that only approximately 260 c.c. is secreted during the first three days, we see that the provided calories fall far below the required amount.

With these facts in mind, it seemed legitimate to attempt in some simple way to meet these requirements, at least in part, and thereby not only lessen the initial loss, but also enable the babies to regain their birth weight more rapidly.

This problem has been attempted by some, but the conclusions arrived at show wide variations. Herrman,[5] in 1915, fed a 10 per cent. lactose solution to 200 new-born infants, and in his conclusions states that he was able to reduce the initial loss of weight from 342 to 186 gm. Sixty-five per cent. of these babies recovered their birth weight by the tenth day of life. He experienced no rise in temperature resulting from inanition, and during the first month no bad results were noted. Ingerslev,[6] in 1875, attempted the feeding of new-born infants by wet nurses; but he concluded that the babies lost more and gained more slowly. Griffeth and Gittings [7] found that when the baby was fed by a wet nurse from birth until the mother's milk secretion was established, the initial loss of weight could be reduced. Keilman [8] found that when artificial feedings were commenced immediately after birth, the infant lost less, but seemed to regain its birth weight more slowly than those nourished solely on the breast. Schick,[9] in 1915, by means of a complemental feeding of mother's milk was able in nine of twelve infants to prevent any initial loss of weight. The feeding was begun from three to six hours after birth and was repeated every two to three hours. An amount equal to from 10 to 15 per cent. of the body weight was given irrespective of what the baby had obtained from the mother. Two of the babies actually gained from the start, and none experienced any ill results. Adair and Steward,[4] who fed a lactose solution to new-born infants, and experienced an average loss of weight of only 7.2 per cent. of the birth weight instead of the normal loss of 9 per cent., concluded that the giving of the lactose solution was of advantage in reducing the frequency of rise of temperature from inanition and in preventing excessive loss of body weight. Ramsay and Alley [10] found that the routine giving of water had little effect on the initial loss of weight, except in those cases in which there was a definitely small amount of milk secreted by the mother. Bruce [11] recently reported the use of powdered milk in early feeding in fifty cases. He was able to reduce the initial loss of weight about 1 per cent. His figures are surprisingly low, in both his control series and the series receiving the ordered food. This he explains by the fact that only those babies who had regained their birth weight before discharge from the hospital (fourteenth day) were included in his report. His final conclusions were that the early feeding did lessen slightly the initial loss of weight, but that these babies recovered their birth weight more slowly.

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[5] Herrman, C.: Should a New-Born Infant Receive Any Thing During the First Two or Three Days? New York M. J., Jan. 9, 1915, p. 67.

[6] Ingerslev: Ueber die Gewichtsverhaltnisse der Neugeborenen, Nord. med. Ark. **12**:7, Part 2, 1875.

[7] Griffeth, J. P., and Gittings, J. C.: Diseases of Infants and Children. Philadelphia, W. B. Saunders Company **1**:21, 1919.

[8] Keilman, A.: Beitrag zu den Erfahrungen über die Künstliche Ernährung gesunder Sänglinge, Jahrb. f. Kinderh., Leipzig, **41**:312, 1896.

[9] Schick, B.: Ernährungs Studien beim Neugeborenen, Ztschr. f. Kinderh. **27**:57 (Nov.) 1920.

It is interesting here to note, as Fishberg [12] has recently done, that the early feeding of new-born infants has been, and is even at present, more generally practiced than one would expect. He states that Soranus of Ephesus, who practiced in Rome during the second century A. D., in a treatise on infants, discourages particularly the use of honey over this period of early postnatal life, showing that this custom was practiced in ancient Rome; also, that, according to Turner, the natives of Samoa offer to their babies a premasticated coconut or sugar cane, and that the inhabitants of the Fiji archipelago resort to a similar practice. In ancient India, new-born infants received honey, butter and various plants containing sugar. He further states that the practice of giving sugar solutions is common among many of the people of eastern and southwestern Europe.

In my investigations conducted at St. Luke's Hospital, my aim was (1) to outline a simple procedure which would not overburden an already busy obstetric ward; (2) to observe to what extent the initial loss of weight could by a simple method be effected; (3) to prevent any enormous early losses, and also to hasten a return to birth weight, and (4) to prescribe various formulas for new-born infants in an effort to estimate, if possible, which was the most efficacious.

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[10] Ramsey, W. R., and Alley, A. G.: Observations on the Nutrition and Growth of New-Born Infants, Am. J. Dis. Child. **15**:408 (June) 1918.

[11] Bruce, J. W.: Complemental Feedings of Dry Milk, Arch. Pediat. **39**: 656 (Oct.) 1922.

[12] Fishberg, Maurice: The Care and Feeding of Infants, Correspondence, J. A. M. A. **80**:421 (Feb. 10) 1923.

METHOD

The prescribed formula was received fresh every day from the diet kitchen or the drug room. The babies were weighed shortly after birth, and thereafter daily before the 10 a. m. nursing. Each baby was put to the breast six hours after birth, and every six hours during the first twenty-four. Following this, the regular four-hour interval was adhered to, including a 2 a. m. feeding. Twenty minutes was allowed at alternate breasts, after which 60 c.c. of the ordered food was offered from the ordinary nursing bottle. Frequently, the smaller infants and those nursing poorly were fed with a medicine dropper.

During the first twenty-four hours, it was rare that an infant took the full 60 c.c., though usually 30 c.c. was taken. On the second and third days, greater amounts were consumed, and frequently the entire quantity. On the fourth day, with the advent of the mother's milk, the larger quantity was again refused. The ordered formula was given through the fifth day, though generally little or none of it was required. At intervals between nursings, water was offered, as is the routine in most obstetric wards.

A few cases of rise of temperature due to inanition were noted, but on investigation it was generally found that these had occurred in the babies who had been nursing poorly and with whom neither the mother nor the nurse had persisted in attempts to establish proper nursing.

The number and types of stools were noted with each new formula, and at no time during the period of investigation was there observed any special deviation from the normal stool of early infancy. This was also true of that period which followed the establishment of the mother's milk. I am convinced that at no time, either in the hospital or after discharge, when the babies are watched in our outpatient department, has any indigestion or bowel disturbance occurred during the early postnatal period from the use of these formulas for new-born infants.

In the reported series are 511 infants, which include both the infants of primiparas and those of multiparas. Only babies definitely normal as far as I could ascertain are reported herein. Among those eliminated from this investigation were those with congenital syphilis, or with suspected cases of cerebral injury; those weaned at birth for one reason or another; some cases of twins in which supplemental feedings had been used, and a small number of premature infants for whom other additional feedings were ordered. The formulas worked with were not devised to meet the actual caloric requirements, but rather to have those calories available as readily assimilable as possible.

RESULTS

Group I. Ordinary Routine Care Without Ordered Food (Table 1). —This group comprised fifty cases taken from the record files of the hospital by the clerk, and included normal cases as indicated by the records. It was chosen merely as a check on the progress of new-born infants prior to the institution of the work which follows. These babies received the usual feedings at four hour intervals, together with sterile water, given frequently between feedings. They showed an average birth weight of 3,135 gm. The weight loss over the first few days was 282 gm. The percentage of body weight lost was therefore 9, or one eleventh of the birth weight. This figure approximates that of other authors. Of these babies, 40 per cent. had regained their birth weight before discharge.

TABLE 1.—*Control Series*

	Birth Weight, Gm.	Loss, Gm.	Percentage	Recovery of Birth Weight, Age (Days)		Birth Weight, Gm.	Loss, Gm.	Percentage	Recovery of Birth Weight, Age (Days)
1	3,628	340	9.3	..	26	3,798	283	7.4	9
2	2,578	255	9.8	9	27	2.840	255	8.9	8
3	3,628	283	7.8	7	28	3,231	255	7.8	8
4	2,352	198	8.3	..	29	3,883	255	6.5	8
5	3,939	510	12.0	..	30	1,870	198	10.0	..
6	3,095	368	11.0	..	31	2,727	170	6.2	..
7	2,868	340	11.0	..	32	1,700	141	8.2	10
8	1,955	226	11.0	7	33	3,345	255	7.6	..
9	3,067	538	17.0	7	34	3,203	170	5.3	..
10	2,783	255	9.1	..	35	2,727	170	6.2	..
11	2,953	340	11.0	9	36	3,123	283	9.0	8
12	3.095	170	5.4	10	37	2,953	368	12.0	..
13	3,769	368	9.7	..	38	3,095	311	10.0	..
14	3,288	226	6.8	12	39	3,316	311	9.0	..
15	3.600	283	7.8	9	40	3,571	340	9.5	..
16	3,345	255	7.6	..	41	3,231	255	7.8	..
17	3,288	198	6.0	6	42	1,899	141	7.4	..
18	4,563	453	9.9	..	43	3,260	255	7.8	..
19	3,741	170	4.5	8	44	3,175	283	8.9	..
20	2,352	198	8.4	7	45	2,783	255	9.1	..
21	3,038	311	10.0	11	46	3,401	453	13.0	..
22	3,769	255	6.7	9	47	3,288	198	6.0	..
23	2,868	311	18.0	..	48	4,563	425	9.3	..
24	3,067	510	16.0	..	49	2,783	255	9.1	..
25	3,288	326	6.8	12	50	3,067	255	8.3	..
Average..						3,135	282	9.0	8*

* Forty per cent. recovered birth weight before discharge.

Group II. Ordinary Routine Care with Definite Orders Regarding the Giving of Sterile Water (Table 2).—I found that when the giving of water was ordered merely routinely and without any definite hours or amounts prescribed, frequently, in the general rush in an obstetric ward, it was neglected. This is especially true in the first twenty-four to forty-eight hours, when a baby sleeps much and cries little, a period during which the giving of any food requires patience and perseverance.

TABLE 2.—*Record of Infants Given Sterile Water*

	Birth Weight, Gm.	Loss, Gm.	Percentage	Recovery of Birth Weight, Age (Days)		Birth Weight, Gm.	Loss, Gm.	Percentage	Recovery of Birth Weight, Age (Days)
1	3,515	113	3.2	7	38	2,897	85	2.5	5
2	3,401	170	4.9	8	39	3,854	226	5.8	..
3	3,231	113	3.4	8	40	2,267	113	4.9	5
4	4,024	283	7.0	..	41	3,684	226	6.1	7
5	3,010	198	6.5	9	42	2,953	368	12.0	15
6	3.401	283	8.3	..	43	3,288	113	3.4	6
7	2,210	226	10.0	..	44	3,095	311	10.0	..
8	3.571	170	4.7	..	45	2,663	340	12.0	..
9	3,203	170	5.3	..	46	3,095	170	5.4	..
10	3,713	226	6.0	..	47	3,010	170	5.6	6
11	3,628	170	4.6	..	48	2,812	340	12.0	..
12	3,628	226	6.2	7	49	2,783	170	6.1	..
13	2,897	198	6.8	9	50	3,628	170	4.6	7
14	2,840	340	11.0	..	51	2,635	198	7.5	13
15	4,422	340	7.6	..	52	3,316	311	9.3	..
16	2,692	198	7.3	9	53	4,450	283	6.3	..
17	3,123	170	5.4	..	54	2,868	198	6.9	7
18	3,571	311	8.7	..	55	4,280	368	8.5	..
19	2,953	226	7.6	7	56	3,571	340	9.5	..
20	3,713	226	6.0	..	57	2,380	56	2.3	4
21	2,783	226	8.1	..	58	3,231	255	7.8	9
22	3,713	226	6.0	10	59	2,982	198	6.6	7
23	3,067	85	2.4	5	60	3,628	255	7.0	..
24	3,231	311	9.6	..	61	1,899	141	7.4	..
25	2,925	170	5.8	..	62	3,175	226	7.1	7
26	3,203	170	5.3	..	63	3,883	226	5.8	..
27	3,288	170	5.1	..	64	3,260	255	7.8	..
28	3,854	340	8.8	8	65	4,082	368	9.0	..
29	3,067	141	4.5	6	66	3,175	283	8.9	7
30	3,911	170	4.3	5	67	1,927	198	10.0	..
31	3,628	170	4.6	8	68	2,267	170	7.4	..
32	3,430	255	7.4	..	69	3,684	396	10.0	..
33	2,783	226	8.1	7	70	2,925	311	10.0	..
34	2,755	141	5.1	9	71	4,082	392	9.7	..
35	2,755	255	9.2	10	72	3,010	283	9.4	..
36	3,123	283	9.0	8	73	2,982	368	12.0	..
37	3,203	170	5.3	9	74	3,231	255	7.8	..
Average..						3,247	229	7.0	7.5*

* Forty-four per cent. recovered birth weight before discharge.

Consequently, I gave definite orders that each infant be offered 60 c.c. of water immediately after the maternal nursing.

In this series, there were seventy-four babies showing an average birth weight of 3,247 gm. The average initial weight loss was 229 gm., or 7 per cent. (one fourteenth) of the body weight. Of these, 44 per cent. recovered their birth weight.

Group III. Five Per Cent. Glucose in Ringer's Solution (Table 3).—Ringer's solution was used because of the presence in it of several of the salts common to those found in the colostrum and mother's milk. The 5 per cent. glucose added makes a food with 10 calories per 30 c.c.

TABLE 3.—*Record of Infants Given 5 Per Cent. Glucose Solution*

	Birth Weight, Gm.	Loss, Gm.	Percentage	Recovery of Birth Weight, Age (Days)		Birth Weight, Gm.	Loss, Gm.	Percentage	Recovery of Birth Weight, Age (Days)
1	3,628	226	6.2	5	46	3,288	255	7.7	..
2	3,713	141	3.7	6	47	3,231	226	6.9	8
3	4,563	255	5.5	..	48	3,345	113	8.3	5
4	3,067	198	6.4	..	49	3,571	255	7.1	8
5	3,316	255	7.6	7	50	3,373	141	4.1	10
6	2,578	170	6.5	7	51	2,897	226	7.1	..
7	3,968	198	4.9	..	52	2,783	113	4.0	8
8	3,741	141	3.7	9	53	1,671	141	8.4	..
9	2,897	198	6.8	..	54	3,316	141	4.2	7
10	3,231	141	4.4	9	55	2,840	226	7.9	..
11	3,458	198	5.6	..	56	2,897	226	7.8	7
12	3,316	283	8.5	..	57	3,175	141	4.4	7
13	3,095	255	8.2	..	58	2,982	170	5.7	8
14	3,345	283	8.4	7	59	3,175	170	5.3	..
15	3,345	141	4.2	7	60	3,010	283	9.4	..
16	2,953	113	3.8	6	61	4,082	396	9.7	..
17	2,635	85	3.2	7	62	3,010	226	7.5	9
18	3,231	170	5.5	7	63	3,430	141	4.1	..
19	3,458	226	6.5	..	64	3,458	170	4.9	..
20	3.038	85	2.7	5	65	2,522	113	4.4	8
21	2,493	141	5.6	..	66	3,543	141	3.9	..
22	3,628	170	4.8	..	67	2,182	198	9.0	..
23	3,373	198	5.8	6	68	3,152	283	8.9	..
24	3,175	113	3.5	7	69	2,210	170	7.6	..
25	3,458	141	4.3	..	70	3,010	113	3.7	4
26	3,175	141	4.4	7	71	3,231	56	1.7	7
27	3,095	226	7.3	8	72	3,684	340	9.2	..
28	3,571	170	4.7	7	73	3,123	141	4.5	6
29	3,486	198	5.6	6	74	3,458	113	3.2	6
30	3,345	198	5.9	7	75	3,798	170	4.4	7
31	3,010	170	5.6	7	76	2,783	113	4.0	7
32	2,897	226	7.8	..	77	2,982	198	6.6	..
33	2,897	170	5.8	8	78	3,373	198	5.8	4
34	2,868	113	3.9	8	79	3,175	283	8.9	..
35	2,755	198	7.2	..	70	2,437	56	2.2	4
36	2,953	85	2.8	..	81	3,911	198	5.0	..
37	3,152	170	5.2	..	82	2,465	170	6.8	7
38	2,493	113	4.5	..	83	2,437	113	4.6	5
39	3,798	226	5.9	8	84	2,925	170	5.8	6
40	3,826	255	6.6	..	85	2,692	85	3.1	9
41	2,783	113	4.0	8	86	3,628	170	4.6	..
42	3,515	198	5.6	...	87	2,783	141	5.0	8
43	2,897	113	3.8	5	88	3,600	198	5.5	8
44	4,167	85	2.3	6	89	3,656	141	4.1	8
45	3,694	283	7.6	..	90	2,755	141	5.2	..
Average						3,179	177	5.5	6.9*

* Fifty-seven per cent. recovered birth weight before discharge.

This solution was fed to the babies in the manner described above, and generally was readily taken. The stools were carefully watched, but no disturbance was noted.

The babies, ninety in number, had an average birth weight of 3,179 gm. Their loss averaged 177 gm.—this being 5.5 per cent. (one eighteenth) of the original weight. In this group, 57 per cent. recovered the birth weight on or before the tenth day.

Group IV. Ten Per Cent. Glucose in Ringer's Solution (Table 4).—With this high sugar content, a bowel disturbance was rather anticipated, but, in spite of careful watching, no change was noted in any one case of the sixty-seven reported.

The average birth weight in this group was 3,231 gm., with an average loss of 165 gm. This proved to be 5.1 per cent. of the body weight, or approximately one-twentieth. The return to birth weight before discharge had occurred in 76 per cent. of the infants included.

Table 4.—*Record of Infants Given 10 Per Cent. Glucose Solution*

	Birth Weight, Gm.	Loss, Gm.	Percentage	Recovery of Birth Weight, Age (Days)		Birth Weight, Gm.	Loss, Gm.	Percentage	Recovery of Birth Weight, Age (Days)
1*	2,812	...	....	1	35	3,067	170	5.5	6
2*	3,628	...	....	1	36	3,038	113	3.8	..
3*	3,095	...	....	1	37	3,826	141	3.7	6
4	3,543	170	5.0	6	38	3,260	85	2.6	7
5	3,430	141	4.1	6	39	3,067	56	1.8	7
6	3,203	113	3.5	5	40	3,345	113	3.4	6
7	4,024	226	5.8	..	41	3,684	85	2.3	4
8	3,741	255	7.1	7	42	3,288	226	7.1	7
9	2,267	85	3.8	5	43	3,175	170	5.5	7
10	1,899	28	1.4	7	44	3,175	170	5.5	6
11	4,053	368	9.0	..	45	2,783	170	6.2	..
12	3,095	283	10.0	..	46	3,713	113	3.1	5
13	2,840	141	5.0	..	47	3,345	170	5.2	8
14	3,175	283	9.0	..	48	4,024	311	8.2	..
15	2,868	141	5.0	7	49	3.288	198	6.2	6
16	3,316	141	4.3	5	50	3,175	141	4.5	4
17	3,515	283	8.2	7	51	3,600	170	4.7	6
18	3,458	226	6.6	..	52	3,401	170	5.0	7
19	3,038	141	4.7	7	53	3,260	113	3.5	5
20	3,968	226	5.8	7	54	3,095	170	5.5	..
21	2,897	141	5.0	6	55	3,288	311	10.0	6
22	3,123	113	3.7	7	56	3,203	141	4.5	6
23	3,401	141	4.1	6	57	3,345	170	5.2	6
24	3,345	255	7.6	9	58	3,288	170	5.2	6
25	3,145	170	5.5	6	59	3,939	255	6.6	7
26	3,203	85	2.6	5	60	3,260	170	5.2	6
27	3,458	226	6.6	9	61	2,578	141	5.5	..
28	3,798	170	4.5	5	62	2,267	170	7.6	..
29	2,663	113	4.3	4	63	2,550	56	2.2	..
30	2,783	113	4.1	5	64	2,692	226	9.0	..
31	3,571	396	11.0	..	65	2,607	28	1.0	5
32	3,175	113	3.5	5	66	3,996	141	3.5	4
33	3,713	255	7.1	6	67	3,038	255	9.0	4
34	2,810	283	11.0	..					
Average......						3,231	165	5.1	5.7†

* No initial loss.
† Seventy-six per cent. recovered birth weight before discharge.

There were three infants who registered no loss whatsoever, and several others with losses less than 2 per cent.

Group V. Albumin Milk (Table 5).—For this, the Merrill-Soule milk was used, the formula being 5 tablespoonfuls to 900 c.c. of water, and included 2 drams of dextrimaltose, which makes a food of about 6.3 calories per 30 c.c.

There was greater difficulty experienced in the giving of this food, since the babies appeared to dislike it, and required considerably more urging. There were seventy-seven new-born infants in this group, with an average birth weight of 3,161 gm. The initial loss was 172 gm., which was found to be 5.3 per cent., or one eighteenth of the birth weight. There were 54 per cent. of the babies who had recovered their birth weight before discharge.

Group VI. Modified Cow's Milk (Table 6).—Whole pasteurized milk was used, together with dextrimaltose (No. 1). A 900 c.c. mixture was prepared with 720 c.c. of water and 180 c.c. milk, which was boiled together for three minutes; after which 2 drams of dextrimaltose was added. The caloric value was about 5 per 30 c.c. The stools were watched, and the only change found was that on the second and third day they tended toward a lighter shade; and also, in general, showed a few small curds.

TABLE 5.—*Record of Infants Given Albumin Milk*

	Birth Weight, Gm.	Loss, Gm.	Percentage	Recovery of Birth Weight, Age (Days)		Birth Weight, Gm.	Loss, Gm.	Percentage	Recovery of Birth Weight, Age (Days)
1	2,408	141	5.8	..	40	3,571	198	5.5	8
2	2,550	28	1.0	8	41	3,288	113	3.4	..
3	3,067	141	4.5	..	42	3,354	170	5.0	..
4	3,123	141	4.5	..	43	3,486	198	5.6	..
5	3,288	141	4.2	8	44	2,840	198	6.9	9
6	3,600	255	7.0	..	45	3,826	198	5.1	7
7	3,231	255	7.8	..	46	3,316	85	2.5	6
8	3,911	283	7.2	..	47	3,203	198	6.1	7
9	3,345	113	3.3	6	48	3,231	255	8.2	..
10	2,408	141	5.8	5	49	3,175	198	6.2	..
11	3,067	198	6.4	..	50	3,769	368	9.7	..
12	2,727	113	4.1	8	51	2,663	113	4.2	7
13	3,095	141	4.5	5	52	2,953	170	5.7	..
14	3,684	226	6.1	7	53	2,465	170	6.8	10
15	3,038	85	2.7	..	54	3,458	368	10.0	..
16	3,741	226	6.0	12	55	2,408	113	4.8	7
17	3,798	170	4.4	7	56	3,095	170	5.4	..
18	3,175	170	5.3	7	57	3,151	198	6.2	..
19	3,123	198	6.3	..	58	2,323	170	7.3	..
20	3,316	198	5.9	..	59	2,897	141	4.8	7
21	2,982	170	5.7	..	60	3,939	255	6.4	7
22	3,316	170	5.1	..	61	3,458	226	6.5	6
23	3,628	141	3.8	5	62	3,067	85	2.4	4
24	3,203	198	6.1	7	63	3,316	113	3.4	6
25	3,203	198	6.1	10	64	2,953	113	3 8	6
26	3,543	226	6.3	..	65	3,095	141	4.5	7
27	2,380	170	7.1	..	66	4,024	283	7.0	..
28	3,741	198	5.2	7	67	2,635	141	5.3	..
29	2,840	170	5.9	8	68	3,123	198	6.3	9
30	2,953	141	4.7	7	69	3,175	226	7.1	..
31	3,345	113	3.3	7	70	3,543	141	3.9	..
32	2,663	226	8.4	7	71	3,010	170	5.6	7
33	2,691	113	4.1	6	72	3,486	170	4.8	..
34	3,095	198	6.4	..	73	2,868	85	2.6	..
35	3,067	85	2.7	..	74	2,267	56	2.4	6
36	2,323	141	6.0	10	75	3,939	170	4.2	..
37	4,053	141	3.4	8	76	2,783	170	6.1	8
38	3,203	113	3.5	7	77	3,458	141	4.0	..
39	2,868	255	8.8	11					
Average						3,161	172	5.3	7.3*

* Fifty-four per cent. recovered birth weight before discharge.

The average birth weight in this group of forty-one cases was 3,078 gm. The initial loss was 152 gm., an average of 5 per cent. (one twentieth) of the birth weight. The recovery of the birth weight occurred in 87 per cent. of the cases.

Table 6.—*Record of Infants Given Modified Milk No. 1*

	Birth Weight, Gm.	Loss, Gm.	Percentage	Recovery of Birth Weight, Age (Days)		Birth Weight, Gm.	Loss, Gm.	Percentage	Recovery of Birth Weight, Age (Days)
1	3,911	85	2.1	4	22	3,571	141	3.9	7
2	2,210	85	3.8	6	23	3,316	85	2.6	4
3	1,643	85	5.1	..	24	3,010	141	4.6	6
4	1,700	141	8.2	..	25	3,345	141	4.2	7
5	3,067	198	6.4	7	26	2,982	113	3.7	5
6	3,713	226	6.0	10	27	3,373	141	4.1	..
7	3,231	255	7.7	10	28	3,067	226	7.3	6
8	3,883	255	6.5	..	29	3,628	311	8 5	6
9	2,727	113	4.1	7	30	3,453	226	6.5	9
10	3,345	141	4.2	7	31	3.693	198	5.3	10
11	3,543	141	3.9	8	82	3,430	255	7.4	10
12	1,870	198	10.0	9	33	2,607	255	9.7	12
13	2,182	113	5.1	10	34	3,515	255	7.2	6
14	2,727	170	6.2	6	35	2,925	170	5 8	..
15	3,543	226	6.3	8	36	2,380	14	...	3
16	2,692	113	4.1	9	37	3,208	56	1.7	5
17	2,727	141	5.1	4	38	3,515	28	...	6
18	3,288	170	5.1	6	39	3,401	56	1 6	3
19	3,095	141	4.5	5	40	3,401	113	3.3	8
20	3,203	170	5.3	..	41	3,288	56	1.3	4
21	2,692	113	4.1	5					
Average......................................						3,078	152	5.0	6.8*

* Eighty-seven per cent. recovered birth weight before discharge.

Table 7.—*Record of Infants Given Modified Milk No. 2*

	Birth Weight, Gm.	Loss, Gm.	Percentage	Recovery of Birth Weight, Age (Days)		Birth Weight, Gm.	Loss, Gm.	Percentage	Recovery of Birth Weight, Age (Days)
1	3,231	141	4.5	6	11	4,337	85	1.9	..
2	3,401	85	2.5	5	12	2,607	113	4.3	6
3	2,607	141	5.5	6	13	3,571	226	6.6	..
4	3,345	226	7.1	15	14	3,175	141	4.5	5
5	4,195	198	4.7	10	15	3,515	170	5.0	..
6	3,316	141	4.3	8	16	2,607	113	4.3	7
7	3,373	170	5.2	8	17	3,175	113	3.5	..
8	3,600	255	7.1	..	18	3,288	198	4.2	8
9	3,123	198	6.6	..	19	3,373	170	5.2	8
10	3,684	198	5.8	..	20	3,713	113	3.1	6
Average......................................						3,361	159	4.7	7.5*

* Sixty-five per cent. recovered birth weight before discharge.

Table 8.—*Record of Infants Given Modified Milk No. 3*

	Birth Weight, Gm.	Loss, Gm.	Percentage	Recovery of Birth Weight, Age (Days)		Birth Weight, Gm.	Loss, Gm.	Percentage	Recovery of Birth Weight, Age (Days)
1	3.010	226	7.6	..	21	4,167	141	3.4	..
2	3,373	170	5.2	7	22	3,571	198	5.5	6
3	3,401	170	4.0	..	23	2,380	113	4.7	7
4	3,798	170	3.7	..	24	2,373	283	9.0	8
5	8,231	198	6.2	6	25	3,486	113	3.3	8
6	2,755	56	2.0	3	26	2,897	170	5.8	..
7	3,231	141	3.4	5	27	3,203	198	6.2	..
8	3,259	198	6.2	7	28	3,401	170	5.0	7
9	3,010	85	2.8	7	29	2,295	141	6.2	10
10	3,203	226	7.1	8	30	2,925	198	7.1	9
11	2,493	113	4.5	7	31	3,038	113	3.8	6
12	3,288	198	6.2	..	32	4,365	255	5.8	12
13	3,288	226	7.1	7	33	3,656	170	4.7	6
14	3,953	283	10.0	6	34	3,684	311	9.0	..
15	3,401	226	6.6	10	35	2,635	198	7.6	..
16	2,663	85	3.2	5	36	2,493	85	3.4	6
17	2,727	170	6.2	..	37	2,465	170	7.1	8
18	3,038	85	2.8	6	38	2,812	85	5.2	..
19	2,607	113	4.3	..	39	3,401	255	7.6	9
20	2,727	141	5.2	10	40	3.152	85	2.6	6
Average......................................						3,096	168	5.4	7.2*

* Seventy per cent. recovered birth weight before discharge.

Group VII. Modified Cow's Milk (Table 7).—In this formula was included 240 c.c. of milk and 660 c.c. of water. Here 3 drams of milk sugar was used, making about 7 calories to 30 c.c. Of the twenty babies on this formula, the average birth weight was 3,361 gm. The loss averaged 159 gm. This was equal to 4.7 per cent. (one twenty-first) of the original weight. There was a recovery of the birth weight in 65 per cent. of the cases. There was no special reason why only twenty babies were given this formula, it being purely a miscalculation on my part.

Table 9.—*Record of Infants Given Condensed Milk*

	Birth Weight, Gm.	Loss, Gm.	Percentage	Recovery of Birth Weight, Age (Days)		Birth Weight, Gm.	Loss, Gm.	Percentage	Recovery of Birth Weight, Age (Days)
1	2,812	141	5.0	..	27	2,982	85	2.8	5
2	2,550	170	6.6	11	28	2,854	170	5.7	..
3	3,010	141	4.6	9	29*	3,316	28	...	9
4	3,798	368	9.6	10	30	3,344	56	1.6	7
5	4,082	170	4.1	7	31	3,826	141	3.6	10
6	2,812	198	7.0	..	32*	3,996	28	...	6
7*	3,713	28	...	6	33	3,543	170	4.7	6
8	3,175	85	2.6	5	34	3,939	141	3.5	10
9	3,095	141	4.5	5	35	3,713	141	3.7	..
10	3,543	113	3.1	6	36	2,925	113	3.8	..
11	2,925	255	8.7	8	37	3,401	113	3.3	7
12	3,486	113	3.2	..	38	2,783	113	4.0	..
13	3,175	170	5.3	9	39	2,578	56	2.1	7
14	2,578	198	7.6	..	40	2,408	141	5.8	6
15	3,175	170	5.3	7	41	2,663	226	8.5	..
16	3,628	170	4.6	10	42	2,323	56	2.4	6
17	2,953	141	4.7	4	43	3,345	170	5.0	14
18	3,123	198	6.3	8	44	2,493	170	6.8	10
19	4,365	368	8.4	..	45	3,316	113	3.4	5
20	3,123	283	9.0	..	46	3,203	85	2.3	4
21	3,203	113	3.5	9	47	3,231	141	4.3	9
22	3,486	141	4.0	7	48	3,203	113	3.5	..
23	3,515	141	4.0	7	49	3,345	56	1.6	7
24	3,401	56	1.6	3	50	2,635	170	6.4	8
25	3,175	141	4.4	8	51	3,458	198	5.7	8
26	3,515	226	6.4	10	52	3,430	113	3.2	5
Average......						3,226	145	4.7	7.4†

* Initial loss less than 1 per cent.
† Seventy-six per cent. recovered birth weight before discharge.

Group VIII. Modified Cow's Milk (Table 8).—Here, 300 c.c. of whole milk were used with 600 c.c. of water. After boiling, 3 drams of milk sugar was added. The stools remained normal.

The average birth weight of the forty infants in this group was 3,096 gm. The initial loss of weight was 168 gm., making a loss of 5.4 per cent. (one eighteenth) of the birth weight. The recovery of the birth weight occurred in 70 per cent. of the cases.

There was noted in a few cases rather abrupt drops in weight, which seemed a warning against any further increase of the cow's milk mixture.

Group IX. Condensed Milk (Table 9).—Eagle brand condensed milk was used, together with water. To 840 c.c. of water was added

60 c.c. of the condensed milk. This made a food of approximately 14 calories per 30 c.c. It was very readily taken, and no bowel disturbances were observed. There were fifty-two new-born infants in this series, and the average birth weight was 3,226 gm.

The initial loss of weight was 145 gm., making an average loss of 4.7 per cent. (one twenty-second). In this group, 76 per cent. returned to the birth weight. There were three infants included whose loss was so small that no percentage loss could reasonably be calculated.

SUMMARY

In the groups described above, there are 511 new-born infants, all normal as nearly as could be ascertained at birth. Group I, a control series, corresponds fairly closely with those generally accepted as normal; the initial loss being 9 per cent., or one eleventh of the original weight, and averaging 282 gm. Restoration of birth weight before discharge from the hospital was accomplished in 40 per cent. of the infants.

Table 10.—*Summary*

Series	Food	No. of Infants	Birth Weight, Gm.	Loss, Gm.	Percentage	Recovery of Birth Weight, Age (Days)	Percentage of these Recoveries
1	Control	50	3,135	282	9.0	8.0	40
2	Sterile water	74	3,247	229	7.0	7.6	44
3	5 per cent. glucose	90	3,179	177	5.5	6.9	57
4	10 per cent. glucose	67	3,231	165	5.1	5.7	76
5	Albumin milk	77	3,161	172	5.3	7.3	54
6	Modified milk No. 1	41	3,078	152	5.0	6.8	87
7	Modified milk No. 2	20	3,361	159	4.7	7.5	65
8	Modified milk No. 3	40	3,096	168	5.4	7.2	70
9	Condensed milk	52	3,226	145	4.7	7.4	76
		511	3,190	183	5.7	7.1	64

The group fed sterile water according to a definite schedule showed some improvement over the control series. The initial loss was 229 gm., 7.1 per cent., or one fourteenth of the birth weight. The recovery of the birth weight occurred in 44 per cent. of the cases before discharge.

Considering, together, the last seven series, all of whom received some type of food and comparing with our control series, we find considerable contrast. These new-born infants show a weight loss of 162 gm., in contrast to 282 gm.; this being 5 per cent., or one twentieth, of the birth weight. Of these infants, 69 per cent. recovered their birth weight before discharge; while in the control series this occurred in only 40 per cent.

CONCLUSIONS

1. The initial loss of weight is produced not only by a disproportion between the intake and the output, but also by the combustion of carbohydrates and fats, which represents a definite caloric requirement besides water replacement.

2. If there is any immaturity of the intestinal tract at birth, or any marked distortion of the bacterial flora after early additional feedings, they are not recognized, in our clinical experience among premature infants or twins, as producing any marked disturbances.

3. With these points in mind, the feeding of formulas for new-born infants seems legitimate, and, judging from the work previously done, harmless.

4. From the cases herein reported, it is perfectly evident that in every group the results showed a definite decrease in the initial loss of weight. This was true even with the giving of sterile water, but under a definitely prescribed schedule.

5. No digestive disturbances were noted in any of these groups, either while the food was given or after the secretion of the mother's milk was established.

6. Also, in checking up recently the records of seventy-five babies who had returned to our followup clinic, and who had come under one or the other of the above-described groups, all showed normal progress and gains anywhere from one month to eight months after discharge.

7. The babies on formulas for new-born infants showed an average loss of 5 per cent., or one twentieth of the body weight, rather than the generally accepted 9 per cent., or one-eleventh. Also 69 per cent. of these babies showed a return to birth weight before discharge from the hospital (usually the tenth day).

8. No definite conclusion seemed warranted as to which type of food is most advantageous, though in this present report the best results were obtained generally with those formulas containing a relatively high sugar content.

9. The conclusion seems warranted, therefore, that the giving of simple formulas to the new-born infant is perfectly justifiable, and that it causes no clinical disturbances. A definite improvement was noted in lowering the initial weight loss, and in hastening the recovery of the birth weight.

THE CALCIUM AND PHOSPHORUS METABOLISM IN RICKETS, WITH SPECIAL REFERENCE TO ULTRAVIOLET RAY THERAPY *

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Chemical studies [1] have made it clear that the defective calcification of the bones in rickets is associated with a diminished concentration of the inorganic phosphorus or the calcium of the serum. Certain cases show only a low inorganic phosphorus content, and this is the rule in uncomplicated rickets; other cases show only a low concentration of calcium, the condition usually found when rickets is complicated by tetany; while still others may be associated with diminished concentrations of both these elements.

It has furthermore been demonstrated that these low concentrations of calcium and phosphorus are found only in the active stage of the disease, and that when rickets heals,[2] either spontaneously or as the result of treatment, the values return to normal.

The more recent work of Howland and Kramer [3] has shown that when the product of the calcium and phosphorus concentrations in the serum is below a certain figure, active rickets is found, and that when the product rises somewhat above this, healing results, with the deposition of calcium phosphate in the bones.

It now seems possible to answer the old question propounded by Lehnerdt: [4] Why does the rachitic bone tissue remain uncalcified? by saying that the bone remains uncalcified just so long as the bone forming elements, calcium and phosphorus, are supplied to it in such low concentrations that precipitation of calcium phosphate cannot take place.

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* From the Department of Pediatrics, Johns Hopkins University, and the Harriet Lane Home, Johns Hopkins Hospital.

1. Howland, John, and Marriott, W. McK.: Quart. J. Med. **11**:289 (July) 1918. Kramer, Benjamin, and Howland, John: Calcium and Phosphorus in Serum in Relation to Rickets, Am. J. Dis. Child. **22**:105 (Aug.) 1921. Iverson and Lenstrup: Første Ved. Nordiske Kongres for Paediat., August, 1919, p. 79.

2. Howland and Kramer: Footnote 1, first reference. Kramer, Benjamin; Casparis, H. A., and Howland John: Ultraviolet Radiation in Rickets; Effect on Calcium and Inorganic Phosphorus Concentration of Serum, Am. J. Dis. Child. **24**:20 (July) 1922. Hess and Gutman: Proc. Soc. Exper. Biol. & Med. **19**:31, 1921.

3. Howland, John, and Kramer, Benjamin: Monatschr. f. Kinderh. **25**:279. 1923.

4. Lehnerdt, F.: Ergebn. d. inn. Med. u. Kinderh. **6**:120, 1920.

There is still to be found an explanation for the low concentrations of these inorganic elements in the blood, and the question naturally arises: Is the deficient calcium or phosphorus in the blood plasma due to an inadequate supply of one or both of these elements in the diet, or is there any impairment of the process of absorption from the intestines?

It is evident that metabolism experiments can furnish the answer to this question. A number of investigators have already conducted such experiments on rachitic children. The most notable work in this field has been that of Schabad,[5] who published a number of papers between 1909 and 1912. At that time, the more refined roentgenologic and chemical methods, now employed to determine whether or not rickets is active, were not in use. He was forced to rely on clinical observations alone to determine this point; and, as we now realize, it is often impossible to tell clinically when healing commences. Thus, certain very contradictory observations may easily find their explanation in a mistaken diagnosis of active or healing rickets.

In spite of occasional exceptions, which we are now able to explain, the large number of experiments which Schabad performed on normal and rachitic infants have made the following facts evident:

On normal diets (chiefly milk), there is a close parallelism between the percentages of calcium and phosphorus which are absorbed. Healthy, breast-fed children retain from 50 to 70 per cent. of their intake of these elements; while artificially fed infants, who receive a somewhat larger quantity, retain in the neighborhood of from 30 to 50 per cent. of each.

With active rickets, only small amounts of calcium and phosphorus are retained, and, not infrequently, the output exceeds the intake.

When rickets heals (either spontaneously or following the use of some preparation containing cod liver oil), large amounts of calcium and phosphorus are retained, sometimes as much as from 60 to 80 per cent. of the amount ingested. Subsequently, there is a gradual return to the normal retention values.

In normal children, the larger part of the phosphorus excreted is found in the urine. In active rickets, owing to the large amount of phosphorus lost in the feces, the percentage of phosphorus excreted in the urine is often reduced to 30 or 40 per cent. The actual amount of phosphorus in the urine is not markedly altered. When healing occurs, there is a striking diminution in the phosphorus lost in the stools, and the percentage of phosphorus excretion in the urine rises to from 50 to 75 per cent., although there may again be little change in the total quantity of phosphorus excreted in the urine. It is evident that under all conditions large amounts of phosphorus are excreted in the urine, and there can be no doubt that this excretion is intimately connected with certain physiologic processes in the body. Thus, it is well known that the elimination of phosphate by the kidneys is a part of the mechanism by which the acid-base equilibrium of the body is maintained, and it is quite possible that there are other functions which may influence this phosphorus excretion.

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[5] Schabad, J. A.: Ztschr. f. klin. Med. **66**:454, 1908-1909; **68**:94, 1909; **69**:435, 1910; Berl. klin. Wchnschr. **46**:823, 1909; **46**:923, 1909; Jahrb. f. Kinderh. **72**:1, 1910; **74**:511, 1911; Arch. f. Kinderh. **52**:47, 68, 1909; **53**:380, 1910; **54**:83, 1910; Ztschr. f. Kinderh. **2**:117, 1911; Monatschr. f. Kinderh. **11**:63, 1912. Schabad, J. A., and Soroschowitch: Monatschr. f. Kinderh. **9**:659, 1911; **10**:12, 1912; Arch. f. Kinderh. **57**:276, 1912.

The excretion of calcium in the urine, on the other hand, is always small. Almost invariably less than 10 per cent. of the calcium lost is found in the urine and sometimes less than 1 per cent. The smallest amount in the urine is found in active rickets. Not infrequently, there is observed in the healing stage an actual rise in the urinary calcium; but this is not pronounced, nor is it constantly observed.

Table 1.—*Before Medication*

	Intake	Urine	Stool	Total Output	Retention	Percentage Retained	Percentage Excreted in Urine
Calcium..........	4.56	0.002	3.64	3.64	0.92	20	0.04
Phosphorus......	4.24	1.320	2.36	3.68	0.56	15	36.00

Table 2.—*After Cod Liver Oil Medication*

	Intake	Urine	Stool	Total Output	Retention	Percentage Retained	Percentage Excreted in Urine
Calcium..........	3.92	0.012	1.04	1.05	2.87	74	1.2
Phosphorus......	3.28	1.36	0.48	1.84	1.44	45	74.0

The experiments of Schabad [6] make it clear that the development of rickets is not to be attributed to a deficiency of calcium and phosphorus in the diet, for a cure of the condition results when they are not increased. Very clearly, the difficulty lies in their absorption. From several of Schabad's experiments, it seems unmistakable that, when rickets heals as a result of cod liver oil therapy, there occurs an increased absorption of calcium and phosphorus from the intestine. Results of a typical experiment are presented in Tables 1 and 2.[7] This

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6. Schabad, J. A., and Soroschowitch: Arch. f. Kinderh. **57**:276, 1912.

7. Figures are given in grams of calcium and phosphorus, recalculated from Schabad's figures for calcium oxid and phosphoric anhydrid. Results are calculated to four-day period.

experiment shows clearly the increased absorption from the intestine and also the increase in the proportion of calcium and phosphorus eliminated in the urine.

The work of Schabad has been confirmed by that of Schloss,[8] who performed a large number of metabolism experiments (1913-1916) on children supposed to have rickets. His results are open to the same criticism as those of Schabad. Only clinical examinations were employed in differentiating active and healing rickets, and a certain amount of confusion resulted. On the whole, most of Schloss's cases of active rickets showed a failure to retain calcium and phosphorus, and the healing cases usually exhibited retention of a large percentage of the ingested minerals.

Schloss's observations with cod liver oil therapy are further confused by the fact that, in several instances, he allowed no time to elapse between the first administration of the oil and the period for the metabolic study that was designed to show the effect of the oil. Only small amounts of calcium and phosphorus were retained in most of these cases; while in all of the experiments in which medication had been continued for a week or more before the metabolism period, high retention values were found. It is quite evident, as has been pointed out, that the effect of the oil is cumulative.

This same failure to allow sufficient time to elapse between the onset of medication and the study of the metabolism led Birk[9] to the conclusion that cod liver oil was practically without specific effect on the metabolism of calcium and phosphorus.

In recent years, the metabolism experiments of Grosser[10] and Telfer[11] have confirmed the fact that active rickets is associated with a diminished capacity of the intestine to absorb calcium and phosphorus, and that, coincident with an improvement in absorption, healing takes place. Neither of these observers made studies of the serum or employed roentgenograms, and consequently mistakes in the diagnosis of active and healing rickets undoubtedly occurred in the work of both.

In all the metabolism experiments hitherto performed in rickets, the only agent which has been shown to cause definite improvement in the absorption of calcium and phosphorus from the intestine has been cod liver oil; and this effect has been obtained in every case when the oil has been given in sufficient quantity, and when sufficient time has been allowed to elapse for its effect to become noticeable. The many experiments in which various salts of calcium and phosphorus have been fed have been most confusing and have given no definite results.[12]

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[8] Schloss, E.: Deutsch. med. Wchnschr. **39**:1505, 1913; Arch. f. Kinderh. **63**:359, 1914; Jahrb. f. Kinderh. **78**:694, 1913; **79**:40, 194, 1914; **82**:435, 1915; **83**:46, 1916. Frank and Schloss: Jahrb. f. Kinderh. **79**:539, 1914; Biochem. Ztschr. **60**:378, 1914; Monatschr. f. Kinderh. **13**:271, 1914.

[9] Birk, W.: Monatschr. f. Kinderh. **7**:450, 1908. Birk, W., and Orgler: Monatschr. f. Kinderh. **9**:544, 1910.

[10] Grosser, P.: Ztschr. f. Kinderh. **25**:141 (June) 1920.

[11] Telfer, S. V.: Quart. J. Med. **16**:45-72 (Oct.) 1922.

In the last few years, as a result of the observations of Huldschinsky [13] and others, it has been found that exposure to radiations from the mercury vapor quartz lamp is strikingly effective against human rickets and the experimental disease in animals. As this agent, the ultraviolet ray, is so dissimilar in nature from cod liver oil, it seemed of interest to investigate the mineral metabolism in rickets before and after ultraviolet ray treatment in order to find out what the mechanism of the curative effect is. Does it promote absorption from the intestine or act in some entirely different manner? It was with this end in view that the experiments here reported were undertaken.

METHODS OF INVESTIGATION

Subjects.—The children selected for this study were male infants with clinical evidences of rickets. Roentgenograms revealed no signs of healing. Chemical examination of the blood serum in all cases indicated active rickets.

Apparatus.—During the metabolism period the children were placed on a frame so constructed that urine and stools could be collected separately.

Diet.—The diet consisted of whole cow's milk or dilutions of cow's milk with sugar added to meet the caloric requirements of each child.

Preliminary Period.—Four days before the beginning of the study the children were placed on the diet to be used and they were kept on this diet throughout the entire period of study.

Metabolism Period.—This was four days in all cases.

Collection of Specimens.—In order to make sure that the stool corresponded accurately with the period of study, the feedings at the beginning and at the end of each period were marked off with vital red. The stools for each period were dried on a steam bath, weighed and subsequently finely ground and put in an air tight container.

The urine was collected every twenty-four hours, and the creatinin determined in order to make sure that no appreciable loss of the specimen had occurred.

Ultraviolet Lamp.—A mercury quartz lamp,[14] with single quartz burner, operating on direct current of 110 volts, was used. This gives one many rays both in the near ultraviolet range, with a wave length of from 400 to 300 millimicrons, and in the far ultraviolet range, with a wave length of from 300 to 100 millimicrons. All radiations were made with a current of 9 amperes at a distance of 18 inches (45 cm.).

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[12] Here may be mentioned the experiments of Birk, Schabad and Schloss, and of Grosser in particular.

[13] Huldschinsky, K.: Deutsch. med. Wchnschr. **26**:712 (June 26) 1919.

[14] Standard model manufactured by Hanovia Chemical & Manufacturing Company.

Plan of Study.—During the first period of four days, the calcium and phosphorus intake and output were determined. The patients were then treated daily for from five to twenty minutes with ultraviolet radiation for a period of from eight to eleven days. Following this, there was a second metabolism period of four days. Roentgenograms at this time revealed deposition of calcium at the epiphyses, and chemical examinations of the serum showed that the calcium and phosphorus concentrations had risen above the zone of active rickets.

CHEMICAL STUDIES

Phosphorus in Milk and Stool.—Specimens of milk and dried stool were ashed with concentrated nitric and sulphuric acids, and the phosphorus was determined by the molybdic acid method.[15]

Phosphorus in Urine.—The phosphorus was determined by the method of Fiske.[16]

Phosphorus in Blood Serum.—The Briggs[17] modification of the method of Bell and Doisy was used.

Calcium in Milk and Stool.—Analyses were carried out on the ash of milk and stool by a slight modification of the method of McCrudden,[18] in that brom cresol purple was substituted for alizarin red as an indicator. Shohl[19] has shown that accurate precipitation of calcium by this method occurs only when the p_H of the solution is between 4.0 and 5.6. The lower limit of p_H was not closely approached when McCrudden's original directions were followed; and by the use of this indicator it was found easy to keep the p_H below the limit of 5.6.

Calcium in Urine.—McCrudden's gravimetric method[18] was used, with the substitution of brom cresol purple for alizarin red as an indicator.

Calcium in Blood Serum.—The method of Kramer and Tisdall[20] was used.

REPORT OF CASES

CASE 1.—P. V., aged 20 months, weighing 21 pounds and 1 ounce (9.57 kg.). had prominent frontal bosses; widely open fontanel; marked rachitic rosary and flaring costal margins, and enlargement of the epiphyses.

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[15] Hawk, P. B.: Practical Physiological Chemistry, Ed. 7, Philadelphia, P. Blakiston's Son & Co., 1921, pp. 570-571.

[16] Fiske, C. H.: J. Biol. Chem. **46**:285 (April) 1921.

[17] Briggs, A. P.; J. Biol. Chem. **52**:349 (June) 1922. Bell, R. D., and Doisy, E. A.: J. Biol. Chem. **44**:55 (Oct.) 1920.

[18] McCrudden, F. H.: J. Biol. Chem. **10**:187, 1911-1912.

[19] Shohl, A. T.: J. Biol. Chem. **50**:527 (Feb.) 1922.

[20] Kramer, Benjamin, and Tisdall, F. F.: J. Biol. Chem. **47**:(Aug.) 1921.

Before treatment the serum determination revealed: Calcium, 9.6 mg. per hundred cubic centimeters; phosphorus, 2.3 mg. per hundred cubic centimeters (product, 22.1).

The metabolism data[21] (four-day period) are presented in Table 3.

Table 3.—*Metabolism Data, Before Treatment (Case 1)*

	Intake	Urine	Stool*	Total Output	Retention	Percentage Excreted in Urine
Calcium....................	5.753	0.044	5.809	5.853	—0.100	0.7
Phosphorus................	4.236	1.185	3.057	4.242	—0.006	27.9

* Total dried stool, 60.224 gm.

After treatment, the serum determinations revealed: Calcium, 10.3 mg. per hundred cubic centimeters; phosphorus, 5.1 mg. per hundred cubic centimeters (product, 52.5).

The metabolism data (four-day period) are presented in Table 4.

Table 4.—*Metabolism Data, After Treatment (Case 1)*

	Intake	Urine	Stool*	Total Output	Retention	Percentage Retained	Percentage Excreted in Urine
Calcium.........	5.154	0.167	2.174	2.341	2.813	54.6	7.2
Phosphorus......	3.784	1.260	0.738	1.998	1.786	47.2	63.1

* Total dried stool, 29.52 gm.

The child did well during the periods before and after treatment. There was no vomiting and no diarrhea. There was a gain of 3 ounces (85 gm.) during the period before treatment and a gain of 3½ ounces (88 gm.) after treatment.

The interval between the first period (before treatment) and the second period (after treatment) was twenty-eight days.

Eleven ultraviolet ray treatments, totaling two hours and fifty-five minutes, were given.

Case 2.—E. T., aged 14 months, weighing 18 pounds and 12 ounces (8.52 kg.) had prominent frontal and parietal bosses; widely open fontanel; rachitic rosary, and enlarged epiphyses. Two weeks before the first metabolism period (before treatment), there had been active tetany. Treatment with ammonium chlorid had resulted in a disappearance of the symptoms, and a marked improvement according to the electrical reactions.

Before treatment the serum determinations were: Calcium, 8.7 mg. per hundred cubic centimeters; phosphorus, 2.5 mg. per hundred cubic centimeters (product, 21.8).

The metabolism data (four-day period) are presented in Table 5.

Table 5.—*Metabolism Data, Before Treatment (Case 2)*

	Intake	Urine	Stool*	Total Output	Retention	Percentage Retained	Percentage Excreted in Urine
Calcium.........	5.921	0.029	5.426	5.455	0.466	7.8	0.5
Phosphorus......	4.352	0.925	3.337	4.262	0.090	2.1	21.7

* Total dried stool, 66.752 gm.

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[21] All results are expressed in grams.

After treatment, the serum determinations were: Calcium, 7.8 mg. per hundred cubic centimeters; phosphorus, 4.6 mg. per hundred cubic centimeters (product, 45.9).

The metabolism data (four-day period) are presented in Table 6.

Table 6.—*Metabolism Data, After Treatment (Case 2)*

	Intake	Urine	Stool*	Total Output	Retention	Percentage Retained	Percentage Excreted in Urine
Calcium..........	5.370	0.151	3.578	3.729	1.641	30.5	4
Phosphorus......	3.853	1.601	1.364	2.965	0.888	23.0	54

* Total dried stool, 40 gm.

The child remained in good condition throughout both periods (before treatment and after treatment), gaining in weight. There was no vomiting or diarrhea.

The interval between the first period (before treatment) and the second period (after treatment) was six days. Eight ultraviolet ray treatments, totaling one hour and fifty-five minutes, were given. The last two treatments were given on the first two days of the metabolism period.

Case 3.—A. S., aged 8 months, weighing 15 pounds (6.82 kg.), had prominent frontal and parietal bosses; a fontanel admitting four finger tips; marked rosary and flaring of costal margins; enlargement of the epiphyses of the wrist; a history of convulsions one week before, and the electrical reactions of tetany.

Before treatment, the serum determinations were: Calcium, 6.0 mg. per hundred cubic centimeters; phosphorus, 3.8 mg. per hundred cubic centimeters, (product, 22.8).

The metabolism data (four-day period) are presented in Table 7.

Table 7.—*Metabolism Data, Before Treatment (Case 3)*

	Intake	Urine	Stool*	Total Output	Retention	Percentage Retained	Percentage Excreted in Urine
Calcium..........	4.270	0.039	3.702	3.741	0.529	12.4	1
Phosphorus......	3.065	1.286	1.624	2.910	0.155	5.0	44

* Total dried stool, 43.958 gm.

Data for the second period (after treatment) are presented in Table 8.

Table 8.—*Metabolism Data, After Treatment (Case 3)*

	Intake	Urine	Stool*	Total Output	Retention	Percentage Retained	Percentage Excreted in Urine
Calcium..........	3.821	0.021	1.901	1.922	1.909	49.8	1.1
Phosphorus......	2.939	1.638	0.445	2.083	0.856	29.0	78.0

* Total dried stool, 29.029 gm.

The child remained in good condition throughout both periods (before and after treatment). There was no loss in weight, and no vomiting or diarrhea. On one occasion, a temperature of 102.5 F. was recorded, but a few hours later the temperature was normal, and did not rise about 100 F. throughout the remainder of the period of operation.

The interval between the first period (before treatment) and the second period (after treatment) was ten days. Ten ultraviolet ray treatments, totaling two hours and thirty minutes, were given.

COMMENT

From the foregoing tables, it is evident that in active rickets there is little if any retention of calcium and phosphorus in the body, and that following treatment with the ultraviolet ray there is a very marked increase in the retention of these elements, one third to one half of the total intake of each being retained.

Our figures show further that, before the rickets was treated, the larger part of the phosphorus, and almost all of the calcium, was found in the stools; while after treatment, much smaller amounts of both these elements were recovered from the feces.

An examination of the figures for phosphorus excretion reveals the fact, first observed by Schabad, that in the healing period there is a marked increase in the percentage of phosphorus excreted in the urine. Whereas in the active period all of our cases showed less than half of the phosphorus excretion in the urine, after treatment from 50 to 75 per cent. was found there. It is quite apparent that this increase in the percentage of phosphorus excretion in the urine is due rather to a diminution of the phosphorus content of the stools than to an actual increase in the amount eliminated in the urine. Thus, in Case 1, the actual phosphorus lost in the urine is almost identical in the active and healing periods, while Cases 2 and 3 showed only a slight increase in the total phosphorus of the urine after treatment.

The effect of treatment on the partition of the calcium excretion between the urine and feces is not very striking. In both the active and the healing periods, the great bulk of the calcium is excreted in the stools. However, it should be noted that Cases 1 and 2 do show an increase in the percentage of calcium excreted in the urine, which is due quite as much to an actual increase in the quantity of calcium found in the urine as to the diminution of this element in the feces. Case 3 failed to show this phenomenon.

From these observations, it seems justifiable to conclude that the ultraviolet rays act by increasing the absorption of calcium and phosphorus from the intestine. It appears likely that absorption of these elements may occur in excess of the amounts which can be utilized for calcification. This slight excess is then excreted in the urine.

It should be pointed out that, while we speak of ultraviolet rays as causing an increase in absorption from the intestine, it is possible that they may act also by decreasing excretion from the intestine. There is nothing in our figures incompatible with this view. We should then have to assume that in active rickets considerable amounts of calcium and phosphorus are absorbed from the bowel and reexcreted into it, and that ultraviolet radiation prevents much of this abnormal reexcretion.

There is evidence [9] to show that when calcium is introduced by subcutaneous injection into a rachitic child it is very largely excreted by the bowel. When phosphorus salts are thus injected,[9] however, no increase in phosphorus in the feces has been found, and most of the phosphorus has been recovered from the urine. It seems unlikely, from these observations, that active rickets is associated with an increased excretion of phosphorus into the intestine, and we therefore feel justified in stating that the healing of rickets is associated with an increased absorption of phosphorus from the intestine.

Since much of the calcium in the intestinal contents is bound by the phosphorus, it seems altogether probable that these two elements are absorbed together, and that ultraviolet light increases the absorption of both of them, rather than diminishes their excretion.

Thus, it would seem that the chief problem of rickets is the absorption of calcium and phosphorus from the intestine. The healing effects of both cod liver oil and the ultraviolet rays appear to be due to their ability to promote absorption from the intestine.

We may thus construct the picture of the rachitic disturbance: The primary difficulty, as yet unexplained, is this defect in the capacity of the intestine to absorb calcium and phosphorus. The low concentrations of these elements in the serum and the defective calcification ensuing are the direct results of this condition. When treatment is instituted, either with cod liver oil or with ultraviolet rays, although no change is made in the calcium and phosphorus of the diet, absorption of these elements from the intestine occurs much more readily. Their concentration in the blood serum rises until the deposition of calcium phosphate in the bones becomes possible.

The mechanism by which ultraviolet light affects absorption from the intestine still remains a problem. It is well known that rays of wave lengths between 400 and 100 millimicrons penetrate the skin to a depth of not more than 1 mm. A direct action on the intestine or its contents, therefore, seems out of the question. One must assume that, as a result of the action of the ultraviolet rays on the skin or on the blood in the capillaries of the skin, the physical or chemical condition of the blood is in some way altered. As a result of this alteration, a greater absorption of calcium and phosphorus from the intestine is produced.

Studies of the effect of ultraviolet radiation on living cells are still in their incipiency. A recent writer on the subject [22] states that the fundamental problem of the mode of action of radiation on the living cell remains unsolved. It seems hardly profitable, therefore, to discuss further the nature of the alteration in the blood produced by ultraviolet radiation and its mode of action.

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[22] Clark, J. H.: Physiol. Rev. **2**:277 (April) 1922.

SUMMARY

1. It is shown by metabolism studies that infants with active rickets fail to retain calcium and phosphorus, although an adequate amount is present in the diet.

2. Ultraviolet radiation causes large amounts of these elements to be retained in the body.

3. Increased amounts of calcium and phosphorus are found in the urine after ultraviolet radiation, indicating an increased absorption from the intestine.

4. It is argued that the defective absorption from the intestine found in active rickets is the cause of the low concentrations of calcium and phosphorus found in the serum, and is the ultimate cause of the defective calcification of the bones.

ATRESIA OF ESOPHAGUS, WITH TRACHEO-ESOPHAGEAL FISTULA *

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Medical literature since the sixteenth century has described anomalies of the esophagus of the type herein reported. In all these years, Hirsch,[1] in 1921, was able to find only 146 authentic cases. Brennemann,[2] in 1913 and 1918, reported five cases seen in a period of five years; while Reynolds and Morrison [3] state that only one such anomaly has appeared in sixteen years at the Bellevue Hospital, and Stukowsky and Boran [4] found only one in a hospital experience covering fifty thousand cases. It has been recently pointed out [2] that the apparent rarity is probably due to failure in diagnosis. We believe that the anomaly is of sufficient rarity to merit the presentation of this case.

REPORT OF CASE

History.—H. E., a boy, aged 5 days, seen in consultation with Dr. James C. Fleming, was the second child, born at full term, after a normal labor, and weighed 7½ pounds (3,402 gm.) at birth. The older child was normal.

There seemed to be nothing abnormal about the baby at first except a profuse discharge of mucus from the nose and throat, which at times accumulated and produced severe suffocative attacks. These were relieved by constant cleansing of the nose and throat.

The mother's milk appeared on the second or third day and the baby took the breast well, but attacks of suffocation would come on while he was nursing. He vomited during or immediately after nursing. Sometimes several nursings were retained without vomiting. The bowel movements contained meconium. The urine was passed in small amounts and infrequently. The baby had lost 2 pounds (907 gm.) since birth. The rectal temperature was slightly below normal.

Physical Examination.—The general examination revealed nothing unusual. There was no bulging of the fontanels and the reflexes were normal. A probe was easily passed through both nostrils. When the tongue was depressed, a large amount of yellowish white mucus came up into the throat. Whenever this was cleaned out and the operation repeated, more of the same material was obtained. A small catheter was passed through the pharynx but met with an obstruction about 1 or 1½ inches (2.5 or 3.7 cm.) below the pharynx.

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* Received for publication, July 17, 1923.

* From the William H. Singer Memorial Research Laboratory and the Allegheny General Hospital.

1. Hirsch, I. S.: Congenital Atresia of the Esophagus, J. A. M. A. **76**:1491 (May 28) 1921.

2. Brennemann, Joseph: Congenital Atresia of the Esophagus, Am. J Dis. Child. **5**:143 (Feb.) 1913; Atresia of Esophagus, Am. J. Dis. Child. **16**:143 (Sept.) 1918.

3. Reynolds, R. P., and Morrison, W. W.: Congenital Malformations of Esophagus, Am. J. Dis. Child. **21**:339 (April) 1921.

4. Stukowsky and Boran: Arch. f. Kinderh. **58**:191, 1912.

The diagnosis of stenosis of the esophagus made by Dr. Fleming was confirmed.

Operation and Outcome.—The patient was removed to the Allegheny General Hospital, and Dr. John Alexander of the surgical staff performed a gastrostomy.

The baby was fed with breast milk through the gastric tube and with peptonized milk by rectum. He did fairly well for several days, then became very cyanotic, and died on the ninth day after birth.

Necropsy.—The neck organs, respiratory organs, diaphragm, liver and stomach were removed *en masse* and carefully dissected out. Aside from the anomaly to be described, there were found Meckel's diverticulum, a bronchopneumonia, and *Streptococcus hemolyticus* bacteremia.

The upper extremity of the esophagus ended in a slightly dilated, blind and rounded extremity 3.5 cm. below the cricoid cartilage and just above the bifurcation of the trachea. This portion reached a diameter of 1 cm. Its extremity was rounded off and its lumen, slightly dilated, reached through its entire length. It was completely separated from the trachea in front. The larynx presented an entirely normal appearance and the formation of the entrance of both larynx and esophagus from the pharynx was normal. There was no connection between the upper part of the esophagus and the lower part. The lower part of the esophagus penetrated the diaphragm in a normal manner. As it was traced upward, it became reduced in diameter and joined the posterior wall of the trachea just above the bifurcation. The trachea was opened and a slitlike fistula was found, which admitted a probe into the lower part of the esophagus. This was found to have a continuous lumen into the cardia of the stomach. The wall of the esophagus merged into that of trachea, and there was no break in the mucosa through the fistula.

The gastrostomy wound was clean and healing, and swabs from the peritoneum were sterile. The heart blood contained a hemolytic streptococcus.

COMMENT

A most striking feature in all these cases is that the clinical symptoms and the anatomic anomaly are always the same. These anomalies are incompatible with life, and treatment of any kind is of no avail. The principal interest in them is found in the treatment and etiology. The only hope for cure lies in surgery. Gastrostomy and jejunostomy have been tried, with complete failure. Richter [5] has devised an operation, which has failed. The fistula into the trachea makes any attempt at feeding by the stomach or small bowel almost sure to fail because of the aspiration of food into the respiratory tract. It would appear that the only procedure which gives hope of cure is one which will correct this feature. Richter's operation is devised to accomplish this end. Early recognition and prompt surgical measures which follow the method of Richter seem the only chance for treatment and cure.

Many theories as to the etiology have been put forward. A brief statement of the various theories will be of interest. Injury to sperm or ovum; trauma to fetus or mother; abnormalities of the placenta; hydramnios; disease in the parents, especially syphilis; atrophy of the esophagus from pressure by the primitive vessels of this region; failure of development of the lumen, and failure of the lower end of the esophageal-tracheal fold to develop have been suggested. The theory of fetal inflammation has received more credence than any of the older views. The presence of an anomaly of all but universal position and type, with no evidence of previous inflammatory changes in the tissues involved has made any inflammatory factor in the etiology impossible. The only tenable theory is that based on a malformation of the anlage of esophagus and trachea.

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[5] Richter: Surg., Gynec. & Obst. **17**:397, 1913.

Briefly, the normal anlage of the respiratory system is a longitudinal groove in the ventral portion of the anterior archenteron, which is gradually separated from the dorsal portion by two lateral and longitudinal ridges (Fig. 1, *L*) which gradually fuse from below (*a*) upward, until the ventral (*T*), the respiratory anlage, is separated from the dorsal portion (*o*), the esophagus. The lungs (c, *L*) develop from buds at the caudal end of the ventral tube and, following lines of least resistance, grow into the anterior body cavity or pleural sac.

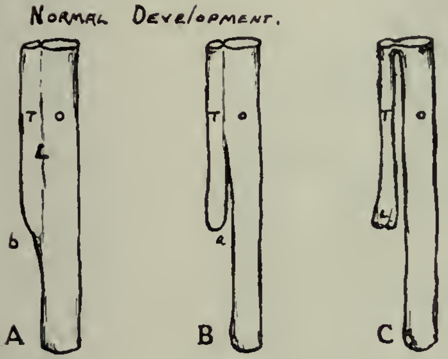

Figure 1

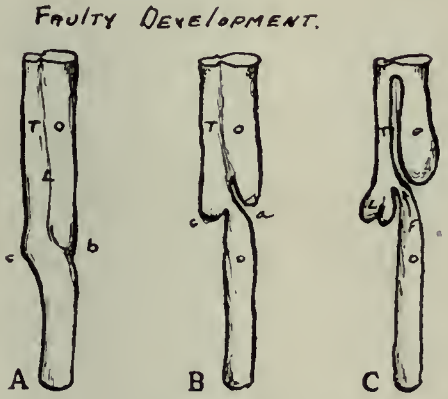

Figure 2

Fig. 1.—Schematic drawing to illustrate the normal development of the respiratory system from the anterior archenteron.

Fig. 2.—Schematic drawing to illustrate the development of the respiratory system in the anomaly described.

The actual mode of development of the present anomaly can only be supposed. The explanation of fistula alone could be easily and logically made; but to show both fistula and complete atresia makes the problem difficult. There must be more than failure of the proper fusion of the lateral ridges. Zeit [6] has put forward a single, simple and entirely logical theory which we accept and enlarge on. We must accept only the hypothesis of a faulty position of the lateral ridges, whose caudal extremity, instead of turning ventrally, tends to turn dorsally (Fig. 2 A, *L*, *b*). Under these circumstances, one would at once suppose that the anlage of the respiratory system would develop dorsally instead of ventrally. However, development in this direction is hindered by the spinal column so that the lateral ridges fuse in a normal manner from below upward, and the anlage of the respiratory system, following the lines of least resistance, develops ventrally into the anterior body cavity (Fig. 2 A and B, *c*). This derangement, as the separation of the esophagus and trachea proceeds, can but leave a blind pouched upper portion of esophagus (atresia) (Fig. 2 C, *o*), and a

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[6] Zeit: J. M. Res. **22**:45, 1912 and 1913.

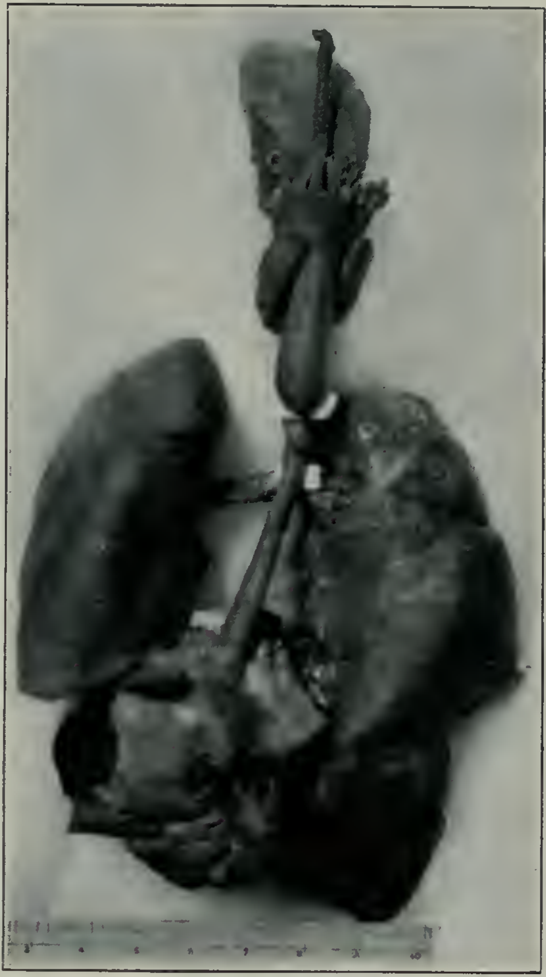

Fig. 3.—Dorsal view of esophagus. The larger, ventral probe enters the trachea and through the tracheo-esophageal fistula enters the lower portion of the esophagus. The dorsal, smaller probe passes into the blind, dilated upper portion of esophagus with its rounded caudal end.

lower portion connected to the trachea above the point of the outgrowth of the lung buds and, therefore, above the bifurcation of the trachea (fistula) (Fig. 2 C). This explanation as suggested by Zeit would logically fit the case of about 75 per cent. of the reported instances of the anomaly, and doubtless, with minor changes, all instances. Beyond this faulty anlage, with our present knowledge, we cannot hope to go.

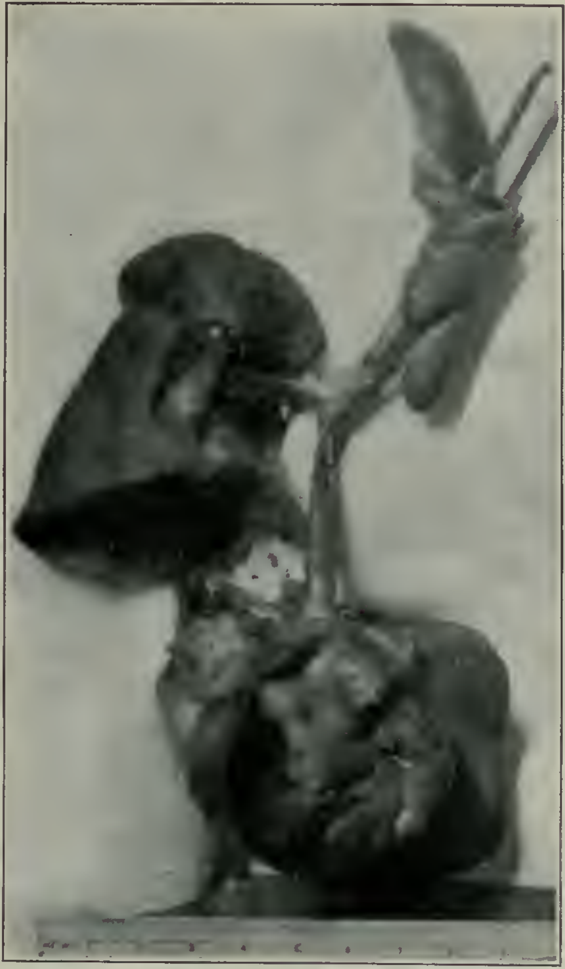

Fig. 4.—A lateral view, showing the relation of the upper blind portion of the esophagus to the trachea in front and the funnel shaped lower portion with its intimate connection with the trachea above the bifurcation. The gastrostomy tube has been left attached to the wall of the stomach.

THE LITERATURE

The first case report found in the literature, according to Hirsch,[1] was cited by Thomas [7] and dated in 1696. Martin,[8] in 1825, reported a case. The literature up to 1884 was reviewed by McKenzie,[9] who found sixty-three instances of malformation of the esophagus. Recently, Kreuter,[10] in 1905, and Plass,[11] in 1917, reviewed the literature, finding 204 cases up to the latter year. Reynolds and Morrison [3] placed the total at 214 in 1921, while Hirsch places it at 146. Steffen [12] and Willard,[13] in 1922, added each another example of the anomaly. Several interesting features are found in the literature. Richter [5] describes an operation designed to cure. Brennemann,[2] in 1913 and 1918, lists five cases and points out the, possibly, only apparent rarity. An interesting review of the various theories as to the etiology is given by Reynolds and Morrison, together with a large bibliography. Cautley [14] has divided the types of malformation into eight groups. From 70 to 75 per cent. of all the anomalies fall into his third group and are essentially like the anomaly here presented. Hirsch points out the uniformity of the picture as seen in reported cases. Other malformations are frequently seen in conjunction with this one. Zeit presents a theory as to the etiology and gives an interesting discussion of the various earlier theories.

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7. Thomas: Anat. H. Body Epitomized, London, 1703.
8. Martin: Obs. d. sc. med., Marseilles, 1825.
9. McKenzie: Manual of Diseases of Throat and Nose, 1884.
10. Kreuter: Ztschr. f. klin. **79**:1, 1905.
11. Plass: Johns Hopkins Hosp. Rep. **18**:259, 1919.
12. Steffen, W. C. A.: Arch. Pediat. **39**:823 (Dec.) 1922.
13. Willard, D. G.: Congenital Atresia of the Esophagus, J. A. M. A. **78**:649 (March 4) 1922.
14. Cautley, E.: Brit. J. Child. Dis. **14**:1 (Jan.-March) 1917.

A CASE OF HEMANGIO-ENDOTHELIOMA OF THE ILEUM*

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The following case is reported because of the rarity of this type of tumor in the ileum and because of the severity of its clinical manifestations. The exact diagnosis is histologic, and we can find nothing in the gross character of the tumor to suggest its nature. Clinically, it is a case of intestinal obstruction in early life. An extensive review of the literature of the last forty-six years yields reports of a similar tumor of the stomach by Cignozzi[1] (1905), Morris[2] (1910) and Sherrill and Graves[3] (1915), but no report of such a tumor in the ileum.

REPORT OF CASE

History.—Betty F., girl, aged 2 months, entered Mount Sinai Hospital because of persistent and continuous vomiting. The family and past history was negative. The present illness began about four days previous to admission with regurgitation of food. At first, only milk curds were regurgitated, but this was soon followed by vomiting of a greenish fluid. Subsequently, it was noticed that the vomitus was fecaloid. There was a complete absence of stools.

Physical Examination.—The child was well built but poorly nourished. The skin was pale, soft, moist and elastic. There was considerable pallor of the mucous membranes. Further physical examination was negative, except for the fact that the abdomen was distended above the level of the ribs. The abdominal veins were very prominent. There was definite pathologic peristalsis, involving the small intestines, which could be plainly seen in intermittent contractions. A tumor mass was not palpated.

Roentgen-Ray Examination.—The barium sulphate entered the stomach normally, but did not begin to leave until three and one-half hours after the ingestion of the meal. At this time, only traces could be observed entering the duodenum. After the stomach had completely emptied itself, a second barium sulphate meal was given in conjunction with a small dose of atropin. The stomach now emptied itself in less than three hours, which indicated that the delayed emptying time was probably due to pylorospasm. The pyloric sulcus was normal. There was, however, marked ileac stasis. Twenty-four hours after the barium sulphate meal, none was seen in the cecum. Normally, all should be in the cecum nine and one-half hours after the meal.

A diagnosis of intestinal obstruction was made.

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* Received for publication, July 19, 1923.

* From the Surgical Service of Mount Sinai Hospital.

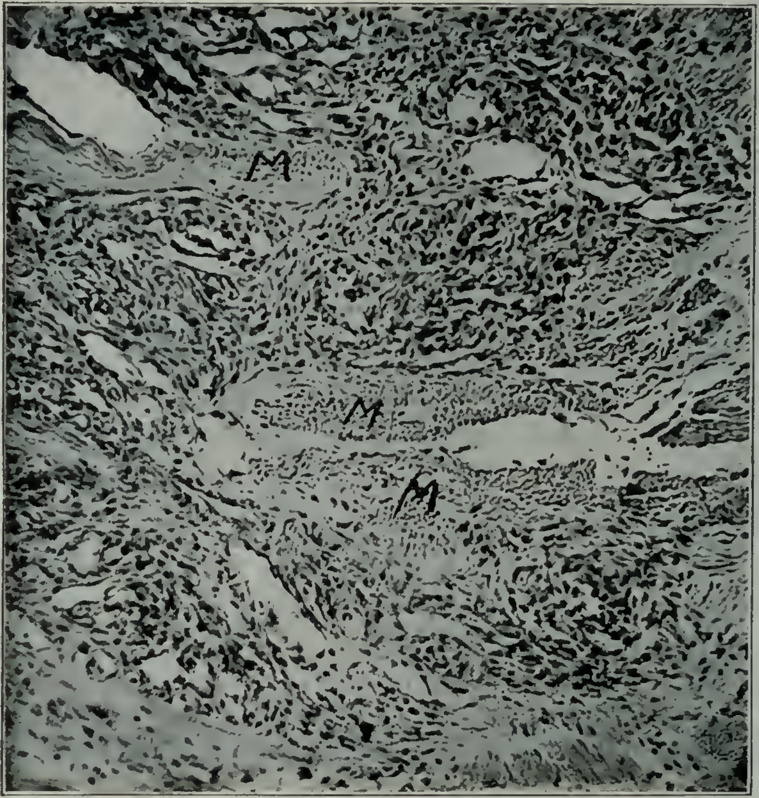
[1] Cignozzi: Endothelioma of Stomach, Riforma Med., July, 1905; abstracted in New York M. J., Aug. 26, 1910, p. 452.

[2] Morris, R. T.: Endothelioma of Stomach, Med. Rec., April 16, 1910, p. 683.

[3] Sherrill, J. G., and Graves, F. S.: Hemangio-Endothelioma Blastoma of Stomach, Surg., Gynec. & Obst. **20**:443, 1915.

Operation.—The abdomen was opened through a high right rectus incision. Exploration revealed a tumor of the consistence of a congenitally stenosed pylorus, constricting the ileum at a point about 18 cm. from the ileocecal valve. Proximal to the tumor, the bowel was greatly distended; distally, it was collapsed. On account of the poor condition of the patient, no attempt was made to resect the tumor. A proximally distended loop of ileum was brought into the incision and an ileostomy performed. The incision was closed in the usual manner, and the bowel opened with a cautery.

Course.—At 3 a. m., the following morning, there was a recurrence of fecal vomiting. Gastric lavage was instituted until clear fluid returned. The patient, however, continued to vomit, and died at 9 a. m.



Photomicrograph (16 mm. lens) showing tumor between muscle (*M*) of intestine.

Necropsy (Dr. John Toomey).—At the reopening of the incision, which was 11 cm. in length, there was no discharge from the wound.

The small intestine was removed from the pyloric end of the stomach to the ileocecal valve. The pylorus was patent, there being, no hypertrophy of the spincter muscle. The lumen of the intestine grew larger as it neared the jejunum, this increase of size beginning about 40 cm. below the pylorus and extending to a tumor mass located 30 cm. above the ileocecal valve. Above the tumor, the intestine was ballooned, the largest diameter immediately above the tumor being 5 cm. The diameter at the tumor area was about 3 mm. From the tumor area to the ileocecal valve, the intestine was normal. Above the tumor, the lower jejunum and ileum showed hyperplasia of lymphoid elements, with some erosion of the surface of a few of the Peyer patches, the intestine containing nothing but gas.

Immediately above the tumor area, there were a few punctate submucous hemorrhages. There was considerable hypertrophy of the intestinal muscle immediately above the obstruction. At the site of the tumor, the lumen was constricted as indicated above, the wall being so invaded that it projected into the intestine, producing the picture of a button-hole stenosis. The intestine in this area could be held in the hand without its collapsing. It lacked elasticity, breaking rather than yielding to pressure. There was congestion around the exterior of the intestine in this region, and the mesentery was mottled by small hemorrhages, reddened throughout and thickened at the attachment to the intestine. There was no free bleeding, no matting of the intestines and no fluid in the abdomen; and the peritoneum showed no demonstrable inflammation.

Microscopic Examination (Dr. H. T. Karsner).—Histologically, the tumor mass was found in the mesentery and in all the coats of the intestines save the mucosa proper. It replaces connective tissue in the submucosa and the muscle of both muscular layers. Toward the lateral margins, the tumor was seen between the bundles of muscle, suggesting an invasive character.

The tumor was lobular in character, each lobule being well defined in the middle of the tumor, but frequently, at the margin of the tumor, showing the lack of boundary line, as seen in malignant tumors, this feature being especially in evidence toward the peritoneal coat of the intestine. The cells of the tumor were large and round, oval or spindle form in most of the lobules, arranged to form vessels of capillary size and slightly larger, containing red blood corpuscles. The capillaries were fairly closely apposed, sometimes with only a single layer of cells, and frequently with several layers of cells interposed. The capillaries apparently formed most irregular whirls throughout the lobules. The tumor cells had a slightly acidophilic nongranular cytoplasm and contained large vesicular nuclei. Careful search failed to reveal mitotic figures, but the nuclei showed considerable condensation of chromatin, the latter being an indication not of mitosis but probably of maturity of the nuclei. The cells were of endothelial character, according to their morphology, and certain lobules showed them collected in fairly large masses, with a few or no capillaries; in which case the histology of an endothelioma was very closely approximated. The stroma of the tumor was extremely scanty, but could be seen as an occasional strand of fibrous connective tissue, with here and there an adult nucleus.

COMMENT

The tumor was obviously a capillary angioma and it appears that the blood content of most of the capillaries justified the term capillary hemangioma. This was associated with a considerable number of endothelial cells, sometimes in fairly large masses. The descriptive term hemangio-endothelioma is therefore employed. If further classification was desirable, it could be said that this tumor should be grouped with the intravascular or simplex class rather than with the peritheliomas.

Ribbert[4] has ruled out many of the previously reported cases because he believes them to be of epithelial origin, and even prefers to abandon the term hemangio-endothelioma and use the term malignant angioma. Borst [5] agrees that the longer and more descriptive term is desirable.

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[4] Ribbert, H.: Geschwulstlehre, Bonn, 1914.

SUMMARY

The tumor here reported is obviously of vascular character, and the most careful examination failed to disclose anything that would justify a consideration of an epithelial origin. The delicate fibrous stroma points also toward the endothelial character of the growth. In this case, as in others, there was nothing to indicate the presence of metastases, and that phase of malignancy is ruled out. Histologic examination, however, revealed that the tumor occupied the entire thickness of the intestinal wall, and there was an associated absence (perhaps disappearance) of muscle. The irregularity of outline, with a fair number of marginal lobules, which showed no definition peripherally, associated with the appearance of endothelial cell collections in the lymphatics of the subserosa, would indicate that, from the microscopic point of view, the tumor was invasive and in that sense locally malignant. From the age of the patient and the character of the tumor, it seems probable that the condition was congenital.

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5. Borst, M.: Die Lehre von den Geschwulsten, Wiesbaden, 1902.

SUBDURAL EFFUSION AND INTERNAL HYDROCEPHALUS

STUDY OF A CASE, WITH RECOVERY *

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The work of recent experimenters, notably Dandy and Weed, has greatly increased our knowledge of fluid circulation within the cranial cavity, providing exact means for the study of cases of hydrocephalus. Application of these methods to each individual problem will frequently point the way to successful therapeutic attack. The case to be presented here was at first indistinguishable from that of a simple obstructive internal hydrocephalus. During the months that it was necessary to keep the patient in the Presbyterian Hospital, I was much indebted to Dr. Howard Mason for help and counsel.

REPORT OF CASE

History.—J. P., an Italian boy, was born of healthy parents at full term, after an easy labor. There were no tuberculous contacts. At 7 months, he began to creep. About this time, there appeared a purulent discharge from the left ear. At 9 months, the first tooth appeared, and the infant was trying to walk. He seemed to be sick and feverish, which the parents attributed to his teething. From this time, development stopped. He made no further progress in walking. At 13 months, he began to have attacks of vomiting, which continued to occur for several weeks, chiefly after meals. At 14 months, it was noted that the baby's head was growing larger and the fontanel, which the mother had thought closed, was found to be open. A month and a half later, two weeks before admission, the eyes crossed; and shortly afterward, the child became blind.

Physical Examination.—The patient was a well-nourished boy of 16 months. The head was disproportionately large, being 52 cm. in circumference. The anterior fontanel was 3 cm. in diameter. There was right internal strabismus. The pupils reacted to light, but the baby gave no evidence of vision. The optic disks were pale and there was a papilledema of from 1 to 2 diopters. The retinal vessels were congested. The deep reflexes could not be elicited, and the abdominal and cremasteric reflexes were absent. Plantar stimulation gave extension of the great toes.

Treatment and Course.—By means of lumbar puncture, 1 c.c. of neutral phenolsulphonephthalein was injected into the lumbar subarachnoid space. An hour later, a needle was inserted into the left angle of the anterior fontanel. It was the intention to puncture the lateral ventricle, but as soon as the point of the needle passed through the resistant dura, fluid appeared and was collected. This fluid contained none of the dye. It was clear and pale yellow in color. The lumbar fluid had been found colorless.

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The next day, a needle was again passed, just through the dura at the same point, this time under ether anesthesia. Forty-five cubic centimeters of amber fluid was withdrawn from a depth of 1 cm. below the scalp, and replaced by an equal amount of air. Vertical and horizontal roentgenograms were then taken of the head in different positions. It was found that the air was not confined in a cyst but passed over the surface of the brain to the frontal poles when the brow was up, and in the reverse position passed back over the occipital poles, clearly outlining the tentorium (Fig. 1). It can be seen in this figure, however, that the passage of air is not altogether free, that there is some adhesion to the brain both anterior and posterior to the fontanel. When the right side of the head was uppermost, some of the air remained on the left side of the falx, where it was injected, and some of it rose and lay over the convexity of the right parietal lobe; while a small amount of air was caught in a corresponding position on the opposite side of the brain.

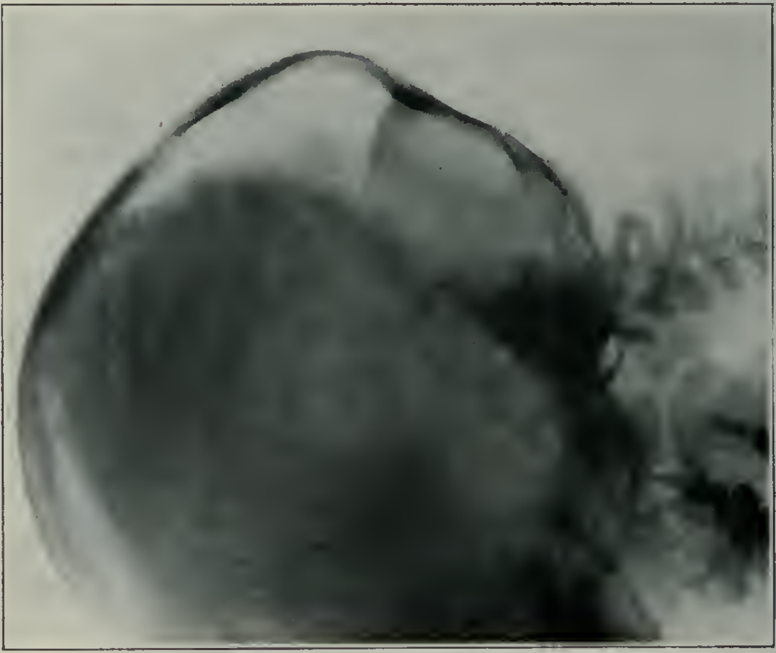

Fig. 1.—Cranial pneumogram after 45 c.c. of subdural fluid had been replaced by air through a needle in the left angle of the fontanel (Dec. 7, 1921); occiput up.

It was apparent that the air was not extradural because it outlined the falx and tentorium. That it was not beneath the arachnoid is evident for the same reason, and because it did not follow the intergyral spaces. The fluid and air must therefore have been situated between the dural and arachnoid membranes in that space, which is normally a potential cavity only. When the subdural injection was made, the air was not put in under pressure. The subdural fluid was simply replaced by a somewhat smaller amount of air. This space had, therefore, been distended by fluid for some time previously.

A week after the first air injection, cranial pneumograms were again made. But this time 40 c.c. of air was introduced into the subarachnoid space by means of lumbar puncture. The air entered the ventricular system and even passed into the basal cisternae and on into the subarachnoid intergyral spaces, where it is represented in the pneumograms by a fine tracery over the convexity of the cerebrum (Fig. 2). Entrance into these spaces was doubtless facilitated by the three previous decompressive taps of the subdural space. Some air still remained beneath the dura.

Thirteen days after admission, the boy could see light for the first time, probably owing to the decompressive punctures. Seven weeks after admission, under anesthesia, dural punctures were made both to the right and to the left of the midline. From the right side came light yellow fluid under high pressure, and from the left, darker yellow fluid. A third needle in the lumbar sac produced clear colorless cerebrospinal fluid. Phenolsulphonephthalein injected through this needle into the subarachnoid space did not appear in either of the other fluids within twenty-five minutes. The conclusion was reached that there was no connection between the fluid cavities on either side of the midline, nor between them and the subarachnoid fluid. This was borne out by pneumography two weeks later, when air was injected into the cavity to the right of the midline, and roentgenograms showed that the air was in the subdural space, as had been demonstrated for the other side by the previous pneumograms. The 45 c.c. bubble of air passed freely everywhere over the convexity of the right hemisphere beneath the dura. Only a very small amount

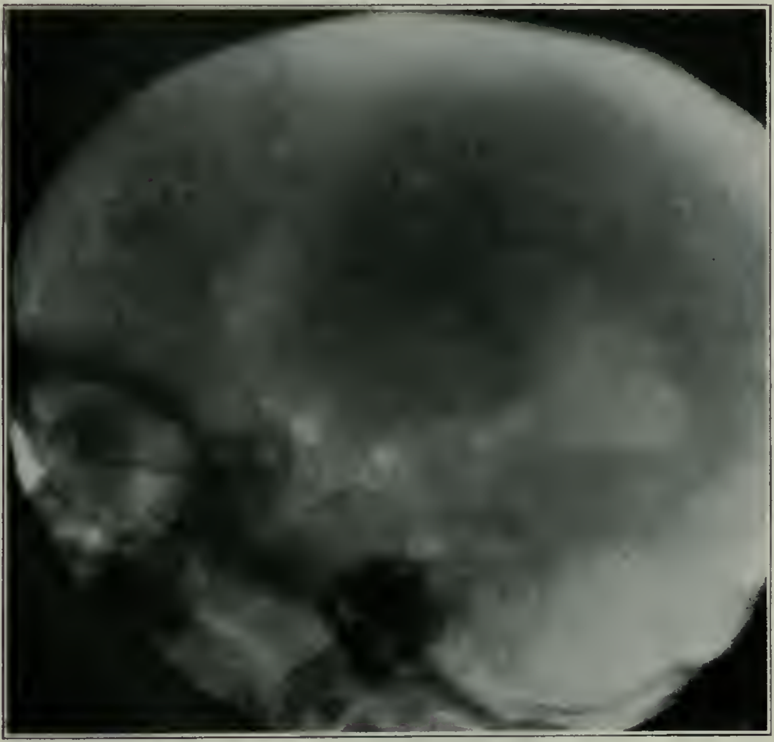

Fig. 2.—Cranial pneumogram after 40 c.c. of cerebrospinal fluid had been replaced by air, through a needle in the spinal subarachnoid space (December 13), right side of head up; air in the right lateral ventricle and intergyral spaces.

passed across to the surface of the opposite parietal lobe (Fig. 3). It is possible that this was a remnant of the air injected eight weeks previously. None was seen in the vicinity of the left side of the fontanel, and this area seems to have been shut off since the first pneumogram. But, when the base of the skull was uppermost, the air did pass freely over the under surface of both frontal and temporal lobes and perhaps the cerebellum as well (Fig. 4).

Pressure observations bore out the conception of the fluids given above. With the boy in a horizontal position, the pressure of yellow fluid in the right subdural space was 360 mm. of water, and that in the left 280 mm. About 5 c.c. of fluid was lost between the two determinations, so that it is quite possible the second reading should be higher. The determinations were made with a manometer connected by coils of rubber tubing to the puncture needles and filled with sufficient Ringer's solution so that, when the manometer was raised, all the fluid which tended to flow out could be returned to its cavity before the reading was taken. Thus, the procedure should not lessen the initial

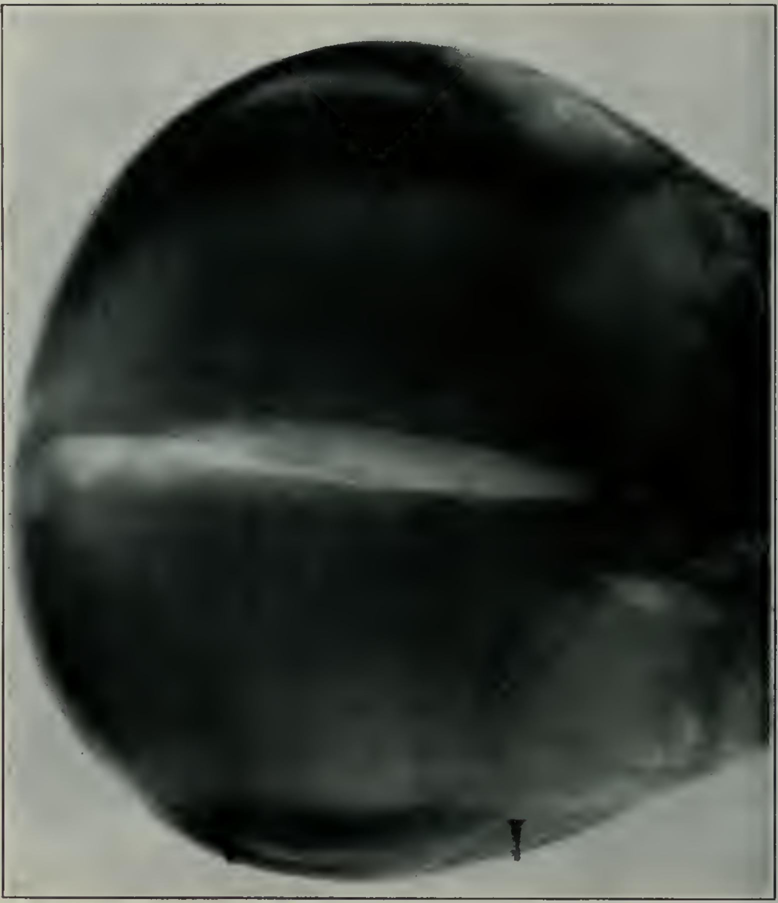

Fig. 3.—Cranial pneumogram after 45 c.c. of fluid in subdural space had been replaced by air through a needle in the right angle of the fontanel (Feb. 3, 1922); right side of head up.

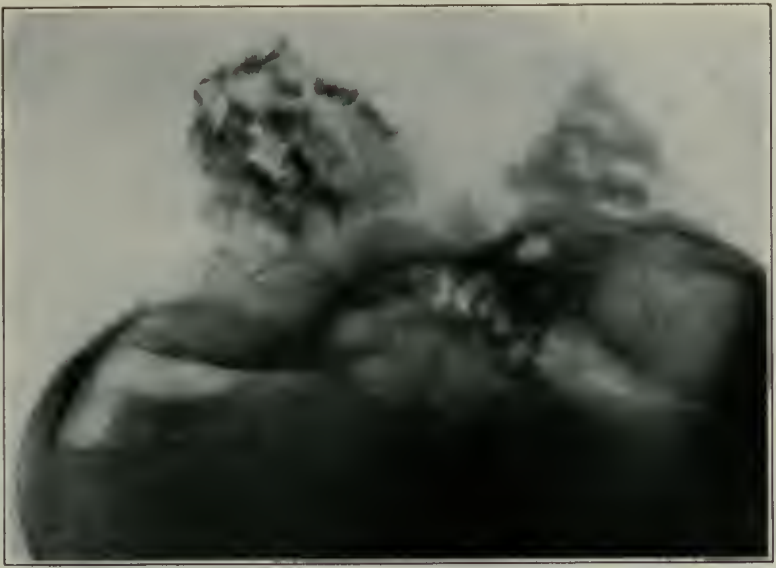

Fig. 4.—Pneumogram taken as in Figure 3; chin up.

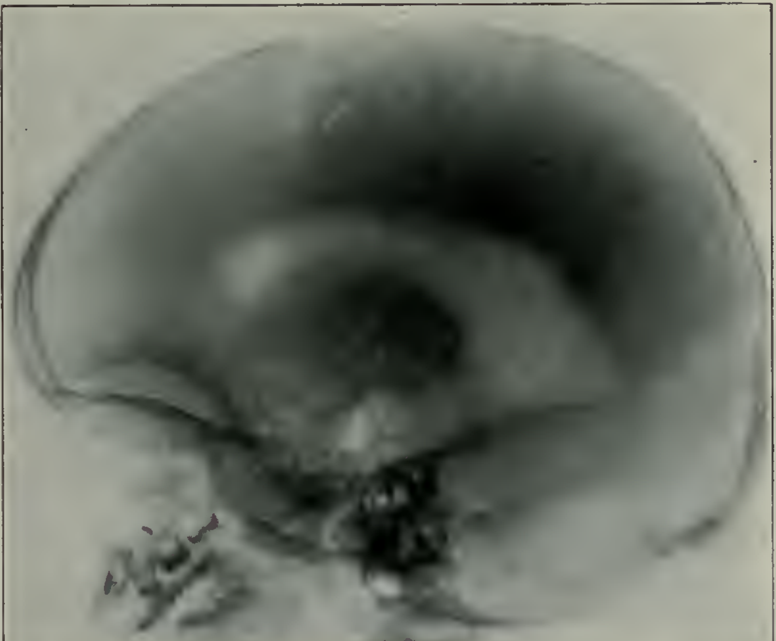

Fig. 5.—Cranial pneumogram after 50 c.c. of cerebrospinal fluid had been replaced with air by lumbar puncture, May 15. Right side of head up; air in lateral ventricles and intergyral spaces.

pressure. With both subdural needles shut off, then, the cerebrospinal fluid pressure was taken by lumbar puncture. This was only 45 mm., a surprisingly low figure. Both subdural needles were opened. Twelve c.c. of fluid flowed from the right and 45 c.c. from the left, while the spinal fluid pressure fell to 10 mm. of water.

The cerebrospinal fluid was always clear and colorless. At the first lumbar puncture, there were 190 cells per cubic millimeter (all lymphocytes), and the globulin was negative. The number of cells rose as high as 3,400 on one occasion (96 per cent. lymphocytes). The cells in the subdural space were generally more numerous, but varied between nine cells and 16,000 cells per cubic millimeter. They, likewise, were all lymphocytes.

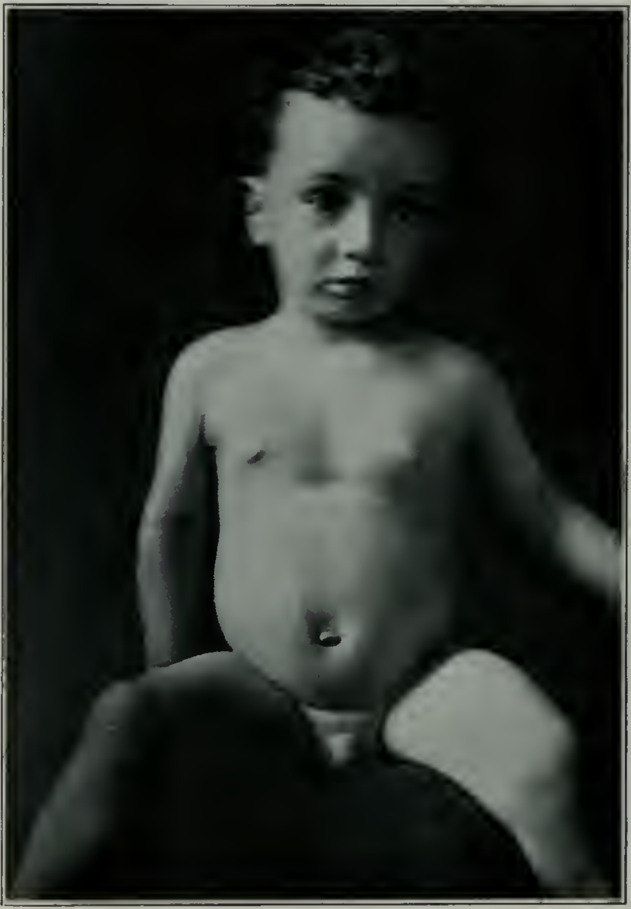

Fig. 6.—Patient at 32 months.

Chemically, the subdural fluid differs very materially from the spinal fluid. For the data in the accompanying table, I am indebted to Dr. Louis Baumann.

The urea nitrogen in the spinal fluid is unusually high, possibly owing to diffusion of this extremely diffusible substance through the arachnoid. The real difference between the three fluids is in the amount of protein and the cell count, both of which are products of inflammatory exudation.

Wassermann tests on the blood and all three fluids were repeatedly negative for syphilis. The Pirquet test for tuberculosis was negative, and injection of both subarachnoid and subdural fluids into several guinea-pigs gave negative results. Cultures of all the fluids were consistently negative.

Outcome.—The patient was discharged in March, 1922, with the expectation of his return for as many subdural taps as might seem necessary. In the following May, he was readmitted. He had improved greatly, had learned to walk, had begun to talk, and could see moving objects. The fontanel was punctured, and 9 c.c. of fluid was obtained from beneath the dura on the left side, and only 7 c.c. from the other side. Air injected into the spinal subarachnoid entered the ventricles, showing them to be still somewhat enlarged. The air escaped freely, however, into the intergyral spaces over the convexity of both hemispheres (Fig. 5).

The boy was discharged from the hospital again and not readmitted. But he has been followed at frequent intervals and now, at the age of 32 months, sixteen months after his first admission, he has grown into an active sturdy lad about equal in development to his brothers and sisters at the same age, according to the parents (Fig. 6). The fontanel is closed, and the head is a little smaller in circumference than when first seen. Intra-ocular and extra-ocular movements are normal, except that there are occasional brief lateral oscillations of both eyes occurring synchronously. Both optic nerves are white, and vision is certainly not perfect, yet he never bumps into things and can pursue a fleeing cat or pick up a penny on a brown floor with unfaltering accuracy.

Comparison of Subdural Fluid with Spinal Fluid (February 3)

	Fluid From		
	Right Subdural Space	Left Subdural Space	Lumbar Puncture
	Yellow	Amber	Colorless
Specific gravity	1.0092	1.0120	1.0054
Nitrogen	0.091%	0.252%	....
Protein	0.569%	1.575%	Trace†
Glucose	0.056%	0.053%	0.055%
Urea nitrogen	0.014%	0.0149%	0.0121%
Chlorids	0.708%	0.704%	....
Globulin	....	....	Very faint trace
Mucin*	....	0	....
Guaiac test for blood*	....	0	....
Oxyhemoglobin bands*	....	0	....

* Test made December 7.
† Test made December 13.

COMMENT

The case has been reported in some detail, as the underlying pathology is considered to be of importance. I have assumed that at 9 months of age there was exudation of fluid into the subdural space, associated with or caused by an inflammatory process which gave rise to the fever reported at that time. The fluid continued to accumulate, giving rise to evidences of cerebral compression; i. e., arrest of development, vomiting and eventual blindness. The pressure was not due alone to expansion of fluid in the subdural space but also, secondarily, to the damming back of the ventricular cerebrospinal fluid by local compression of the subarachnoid pathways beneath, in the sulci on the surface of the brain. This is borne out by the moderate degree of distension of the ventricular system seen in the pneumograms (Fig. 5) and by the fact that the elimination of dye from the cerebrospinal fluid was below the normal rate.

There is no pathologic incident to be discovered in the boy's history except otorrhea on the left side. Moreover, he presented otoscopic evidence of having had middle ear disease on both sides. It is difficult to be sure how long after the onset of the otitis the exudate appeared in the subdural space, but the secondary effects of pressure became evident within about two months. There is no evidence of other infection. It is difficult, therefore, to escape the conclusion that the subdural effusion is causally as well as temporally secondary to the otitis media.

If the primary process was a chronic mastoiditis, which occasionally became acute, the explanation of the six sharp temperature rises during the stay in the hospital is evident. Some of these rises, possibly all, were associated with a leukocytosis with high polymorphonuclear count; while the cellular reaction in the subdural and cerebrospinal fluid was, as has been said, wholly lymphocytic. Clinically, the mastoid was looked on with suspicion at one time, but operation was never considered justifiable. In retrospect, it would seem better, with a clear picture of the probable process in mind, to address one's efforts toward clearing up the primary focus, rather than to be content with preservation of the eyesight by means of repeated aspiration, until the primary process terminates spontaneously.

Without going into the literature at present, it is interesting to recall that Gradenigo[1] pointed out the frequency of the association of acute otitis media with paralysis of the adducens nerve, vomiting and optic neuritis. Barr and Rowan[2] showed that, of 160 cases of otitis media, 6.8 per cent. had a choked disk and 25 per cent. presented lesser vascular changes of the retina. These clinical statistics must have a mechanical explanation. Subdural fluid under tension, as proved in the case presented here, offers such a mechanical basis for an increased intracranial pressure. The pneumographic study of this case may likewise suggest an explanation of the association of middle ear disease with serous meningitis, and provide a reasonable pathologic basis for the latter condition.

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[1] Gradenigo: Arch. f. Ohrenheilk, **74**, 1907.

[2] Barr, J. S., and Rowan, J.: Optic Neuritis and Suppurative Otitis, Brit. M. J. **1**:737-42, 1910.

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INCIDENCE OF DISEASE IN ONE THOUSAND INFANTS UNDER TWO YEARS OF AGE *

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The importance of infant mortality statistics is now recognized in all parts of the civilized world. They play so important a part in every problem confronting the nation that voluminous books and reports have appeared analyzing mortality figures and suggesting methods of decreasing mortality. Very few, if any, comprehensive studies have been made of infant morbidity so far as we know, and yet this important field deserves investigation because death is nearly always preceded by disease. If accurate figures, from which to study the incidence of disease, were available and were recorded in such a way that the causes and influences which are responsible for illness could be analyzed, many factors of importance would undoubtedly come to light.

Ashby [1] emphasizes the fact that "infant sickness not only leads to a deplorable waste of human life, but also sows the seeds of weakness, deformity and impaired vitality in those who survive to take their share in the duties of citizenship, and it contributes in no small degree to the physical degeneracy of the race, which we can see only too plainly taking place around us in the large cities."

Unfortunately, morbidity records are available only in a few institutions, and the fact that they are institutions precludes at the onset comparisons and deductions which could be applied to the general public. We have taken the records of the Boston Baby Hygiene Association as representing a cross section of the poorer classes of the city of Boston who are living in their own homes. The records were kept by physicians running the health stations for well babies, and represent their observations.

This study is based on 1,000 of these records, selected at random. They do not represent any particular years, but all of the infants had graduated from our care. None of these infants came under observation until 2 weeks of age. This was due to the fact that before that time they were under the care of the obstetrician. As a result, all the dis-

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[1] Ashby: Infant Mortality, Cambridge Public Health Series, 1915.

eases of the new-born infant have been eliminated from this series. These children lived under conditions obtaining in families in which welfare work is usually done.

The record of each infant was abstracted and analyzed as far as possible with the material at hand. That the analysis is in some respects incomplete is due to the fact that the records were originally kept for the purpose of routine clinical work and were not designed as the basis of statistics.

Of the 1,000 infants, fifty-one died. This mortality rate compares favorably with that of the city of Boston for the years 1916 to 1920 inclusive, but does not represent the mortality of the Baby Hygiene Association for that period. The cause of death was unknown in seventeen instances. Sixteen of the remaining thirty-four infants died of pneumonia. Of the remaining eighteen cases, the cause of death was divided among the various diseases. It was surprising that diarrheal diseases did not play a greater part in the mortality of these children because it usually appears as a common cause of death, yet out of the 204 cases of diarrhea there were only four deaths. As would be expected, the death rate among the prematurely born was high. Of ten premature infants, three died. Of seven children who contracted diphtheria, three died.

INCIDENCE OF DISEASE

The relation of morbidity to mortality is of importance. Of the 465 infants who had some disease, fifty-one died. The morbidity rate is about nine times as great as the mortality rate.

Five hundred and thirty-five of the 1,000 infants were entirely free from disease during the time they were under observation. This varied from twelve to twenty-four months. Of these 535 cases, 59 per cent., or 318, were entirely breast fed during the whole of their first year of life; while the majority of the remaining 40 per cent. were breast fed for at least six months.

Of the infants that were bottle fed entirely, 36 per cent. had no disease during the first year, while the remaining 64 per cent. had some disease. This shows conclusively that there is a much greater chance of illness in the bottle-fed than in the breast-fed infant. Since many uncontrollable factors also play a part in these results, we cannot go further on this evidence and conclude, as we should like to, that this proves that human milk contains substances which prevent disease.

Great emphasis is laid on the seasonal influence on infant mortality. The morbidity of this group has consequently been plotted for the different months of the year. This is presented in Chart 1, which shows a great increase in the incidence of disease during the summer months, and whose curve is thus comparable to curves showing the seasonal incidence of infant mortality. The great increase of disease during the summer months is largely due to the incidence of the diarrheal diseases, 41 per cent. of the cases in July and 81 per cent. of the cases in August being due to diarrhea. The other two outstanding diseases which were prevalent to a lesser degree during the months of August to December inclusive were measles and pneumonia. Unfortunately, it was impossible to obtain also a record of the incidence of head colds. Pertussis was present throughout the year. Pneumonia was most prevalent in January, February and March, in which 51 per cent. of the seventy-two cases occurred. Measles was most prevalent during April, May, June and July. Seventy-seven per cent. of the sixty-five cases occurred during these months.

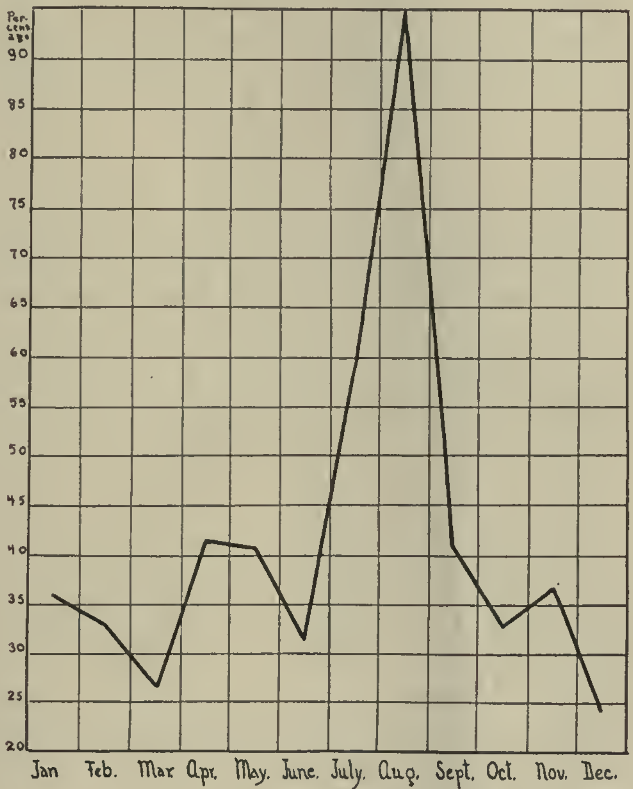

Chart 1.—Seasonal incidence of morbidity

Measles: Three of the fifty-two cases of measles were in infants younger than six months. Since the two types of measles were not differentiated in the records, it is possible that these three cases were rubella. There is considerable evidence for the belief that an infant under 6 months never contracts measles. These figures at least indicate that there is little likelihood that measles will be contracted before the sixth month.

Incidence Among Breast Fed and Bottle Fed.—It is a well known fact that the mortality of breast-fed infants is lower than that of bottle-fed infants. That the same difference is to be observed in their morbidity is indicated by the following figures: Five hundred and thirty-five infants, or 53.5 per cent., had no disease. Of these, 318, or 31.8 per cent., were entirely breast fed, and 266, or 26.6 per cent., only partly breast fed or entirely bottle fed.

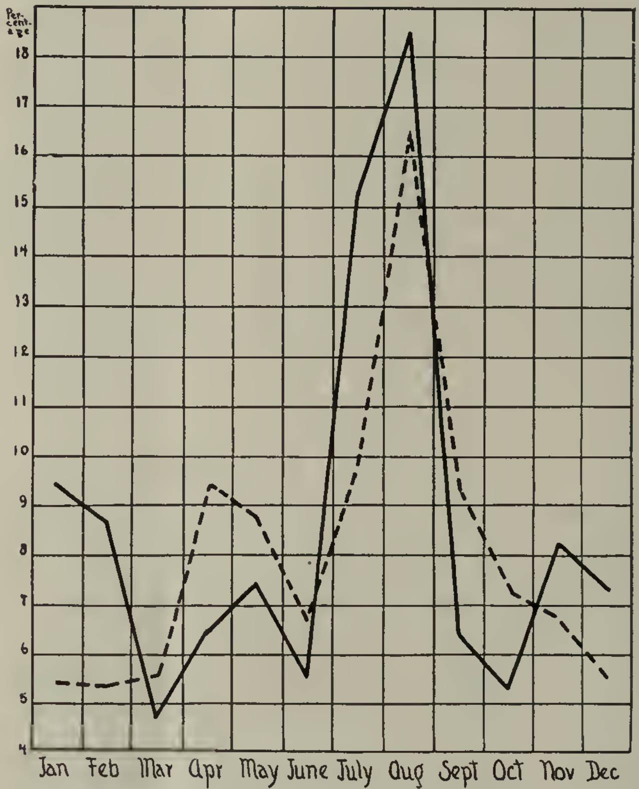

Chart 2.—Morbidity in infants with (solid line) and without (broken line) brothers and sisters of school age.

Of 465 cases, or 46.5 per cent., of all the infants that had any illness of any sort, 212, or 45 per cent., were entirely bottle fed, and the remainder had received some breast milk during the first year.

Incidence Among Those With and Without Brothers and Sisters of School Age.—It has frequently been stated that older children in the family act as carriers of disease and probably raise the morbidity rate of their infant brothers and sisters. Of the 465 infants who were ill, 264, or 56.7 per cent., had no brothers or sisters of school age.

Chart 2 represents the percentage distribution of the total number of cases of illness during the months of the year, contrasting infants having brothers and sisters of school age with those not having them.

No certainly valid explanation of the excess of morbidity among infants without brothers and sisters of school age can be given from the data available. It is possible, however, that, in caring for the first baby, lack of experience on the part of the mother and lack of opportunity for receiving training are factors. On the other hand, data is not available to show the total number of adults in these families, and an unusually large family of adults may have meant a greater opportunity for the carrying of infection in some instances.

CONCLUSIONS

Infant morbidity shows a similar curve to that of infant mortality. Of each nine children of this group who contracted disease, one child died. The principal causes of death were pneumonia and diphtheria. The mortality due to diarrhea was relatively low, about 2 per cent. This is a marked improvement over the mortality figures of a decade earlier.

A breast-fed infant is much less likely to contract disease than a bottle-fed infant. This, added to the greater likelihood of recovery if the infant does become ill, is an additional argument for maternal nursing.

RECURRING CARDIAC INFECTIONS IN CHILDREN WITH CHRONIC VALVULAR DISEASE*

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During the last three years, eighty cases of chronic valvular disease in children have been followed in the cardiac clinic of the Central Free Dispensary of Rush Medical College. Twenty-one of these patients, who have had, on frequent occasions, a slight temperature, ranging from 99.2 to 100.4 F., have been carefully observed for recurring cardiac infections, and the rate of progress of their cardiac disability has been compared with that of the remaining fifty-nine children. The twenty-one reported to the clinic, on the average, once every two weeks. The period of observation varied from four months to three years.

The ages of the twenty-one children ranged from 5 to 12 years. Eight had no particular complaint. They were requested to return to the clinic at frequent intervals because of the temperature findings. The remaining thirteen tired easily, and the majority had poor appetites. Seven complained of an occasional precordial pain. In two, the pain was so severe that it awakened them from their sleep. Eight of the thirteen were at some time during the period of observation short of breath on slight exertion. Three of these had attacks of cardiac failure.

In six instances, there was a history of rheumatic fever. Four others had indefinite pains in the legs. In two, these pains recurred during periods of fever. In another, the pain in the leg was first noticed after the child had been having slight temperature at frequent intervals for several weeks. Two had had chorea. In one, the chorea was associated with tender joints. Fifteen of the twenty-one had had the tonsils removed. Five of these gave a history of frequent sore throats before the operation. None of these children had had rheumatism. Five of the six who still had their tonsils had a cervical adenopathy. In four of these, the tonsils have since been removed.

INCIDENCE OF RECURRING CARDIAC INFECTION

Three children had complete heart block. In two, the auriculoventricular dissociation lasted only a few days and was associated with

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* Received for publication, Aug. 8, 1923.

indefinite pains in the legs. These children are now apparently in good health. The third child still has a delayed conduction over the auriculoventricular bundle. The conduction defect was first discovered about nine months ago. During this period, she has had a slight temperature most of the time. About three months ago, she complained of pains in her legs for the first time, and one knee was definitely tender. She is pale and thin and has a poor appetite. The pulse rate has continually been rapid and the heart very irritable. The size of the heart has gradually increased. The apex impulse six months ago was about the nipple line. Now it is at the anterior axillary line.

In four other children, the electrocardiograms showed a transient prolongation of the P-R interval. None of these patients was taking digitalis. In two, the electrocardiographic findings were the most suggestive evidence of a recurring carditis. The other two have large hearts. Each complained of frequent pain in the precordium. One had, for a few days, a to and fro murmur, which was thought to be a pericardial friction rub. Both had at one time a definite cardiac dilatation. One of these has rapidly improved during the last few months. He now has no complaints and looks well.

Two other children had premature contractions during periods of temperature. In each instance, the irregularity disappeared after the temperature subsided. One later showed an increase in the size of the heart and in the intensity of the systolic apical murmur.

In two children, the diastolic murmur of aortic regurgitation developed within the last few months. One of these was first seen about six months ago. He had a mild mitral regurgitation and was apparently in good general health. He returned to the clinic six weeks later with a rise in temperature. He reported thereafter at weekly intervals that we might check the temperature and cardiac findings. The fever persisted, and within a few weeks a faint diastolic murmur was heard to the left of the sternum in the third interspace. During the last two months, the murmur has markedly increased in intensity, and the apex impulse is now well outside the nipple line.

In five other children, the cardiac damage has rapidly progressed during the last year. It is difficult to explain this rapid progression except on the basis of an active infection in the heart. One child was first seen seven months ago. According to the mother, the child had had a slight cardiac lesion for more than a year. At the time of the first examination, the apex impulse was about the nipple line and a soft systolic murmur was heard at the apex. Now the left border of the cardiac dulness is well outside the anterior axillary line. There is a to and fro murmur at the apex and a gallop rhythm. This child has had fever most of the time. She has been hospitalized twice for periods of two and three weeks. On each occasion, the temperature subsided after three or four days of absolute rest. On the return to the clinic, however, fever was again noted.

The determination of an active cardiac infection in a child with chronic valvular disease may be very difficult. Recurring periods of slight temperature which cannot be explained on the basis of an ordinary acute infection, especially when associated with a rapid pulse and an irritable heart, should arouse suspicion. The child may make no complaint, and the rise in temperature may be discovered accidentally. There may be no changes in the character of the murmurs resulting from previously damaged valves. The heart may be large and there may be slight degrees of dilatation difficult to detect. It may be weeks before more definite manifestations, such as a new murmur, a pericardial rub or demonstrable cardiac dilatation, appear. The electrocardiograph frequently enables us to make a diagnosis earlier in the course of the infection. Seven of our patients showed conduction defects of the auriculoventricular bundle before other definite evidence of cardiac infection could be demonstrated. In two children, the transient auriculoventricular dissociation was the only definite manifestation of further damage to the heart. It is not unlikely that even more transient conduction defects would have been discovered had more frequent electrocardiograms been taken early in the course of our observations.

In this connection, it may be added that in 1920 Eyster and Middleton [1] reviewed the literature on heart block in children and found that twenty cases had been reported. In nine of these, a congenital lesion was probably responsible for the conduction defect. No doubt as instruments of precision become more generally employed, the incidence of transient heart block in children will be found to be much greater than is indicated by the literature.

It is well known that individuals with chronic valvular disease may have recurring cardiac infections. The importance of these recurring infections in the progression of cardiac disease is apparently not generally appreciated. In our eighty patients, the incidence of extensively damaged hearts and the rate of the progression of the cardiac disease was far greater in the twenty-one with recurring infections. Two have died from cardiac failure during the last six months. Another is in the hospital and is not expected to recover. In seven others, the cardiac disease is of the rapidly progressive type, and the patients now become short of breath on slight exertion. Among the remaining fifty-nine, on the other hand, there are, to our knowledge, no children with symptoms of cardiac failure. Twelve of these had fairly extensively damaged hearts. They were, however, in this condition when first seen in the clinic and the condition has apparently not progressed to any great extent. These children have been free from fever except that which could be attributed to an occasional cold. Forty-seven of the fifty-nine have a minor or a moderate cardiac disability. The majority of them were in splendid physical condition when last seen.

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[1] Eyster, J. A. E., and Middleton, W. S.: Auriculoventricular Heart Block in Children, Am. J. Dis. Child. **19**:13 (Feb.) 1920.

One of the difficult problems of the physician in the management of a child with chronic valvular disease is in preventing the lesion from progressing. Rheumatic fever frequently recurs and the heart is subjected to further infection. In some instances, the rheumatism may return in such an insidious form that it is overlooked by the parents, and yet the heart is seriously damaged. No doubt a great deal can be accomplished by educating the public. They should know that a recurrence of the rheumatism may mean a reinfection of the heart. They should be taught that what is ordinarily known as growing pains is often rheumatism. Instruction as to diet, fresh air, sunshine and proper clothing is very necessary in many instances. The importance of consulting the physician whenever there is doubt as to the condition of the child should be emphasized. Infections would in most instances be recognized earlier, and the child would be given proper treatment at a time when it was most beneficial. Even though the child with chronic valvular disease is apparently in good health, the condition should occasionally be checked by the physician.

The prevention of further infections by the removal of adenoids and diseased tonsils, and the extraction of infected teeth is very important. It is generally known that tonsillitis may precede the onset of an attack of rheumatic fever. St. Lawrence [2] has, in a carefully conducted investigation, shown that the incidence of the recurrence of rheumatism is much less in those children in whom the tonsils were carefully removed. In our patients, those in whom the cardiac disease was most progressive had definitely infected tonsils with cervical adenopathy. Poynton [3] has called attention to the frequent occurrence of cervical adenopathy in children with rapidly progressive rheumatic carditis and believes that, in these instances, the tonsils undoubtedly contributed to the infection.

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[2] St. Lawrence, William: Effect of Tonsillectomy on Recurrence of Acute Rheumatic Fever and Chorea, J. A. M. A. **75**:1035 (Oct. 16) 1920.

[3] Poynton, F. J.: Cardiac Infections in Childhood, Brit. M. J. **1**:249 (March 2) 1918.

The treatment of cardiac infections would be improved by the establishing of convalescent homes. The infection may persist for months, and no doubt the rest period is frequently not sufficiently extended. This is often not possible in the hospital where room has to be reserved for the more acutely ill patients. Furthermore, the carefully supervised regulation from the standpoint of rest is impossible in the home of the patients who visit the outpatient clinics. The convalescent home would thus bridge over one of the greatest defects in the present treatment of cardiac infections and would no doubt decrease the incidence of severely damaged hearts in children.

SUMMARY

1. Eighty children were followed during the last three years. Twenty-one (26 per cent.) had frequent periods of slight fever ranging from 99.2 to 100.4 F. In sixteen of these, the diagnosis of an active cardiac infection was made. In seven instances, the diagnosis was based on the finding of a conduction defect of the auriculoventricular bundle. Two had premature contractions during periods of fever, one of whom later had definite cardiac dilatation. In the remaining seven, the conclusions concerning the presence of a cardiac infection were based on definite changes in the physical findings of the heart, such as the appearance of a new murmur, a pericardial rub or demonstrable cardiac dilatation.

2. The rate of progression of the cardiac disease was much more rapid and the incidence of severely damaged hearts far greater in the twenty-one children with recurring periods of temperature than in the remaining fifty-nine.

3. The diagnosis of active cardiac infection in children with chronic valvular disease may be difficult, and several weeks may elapse before definite manifestations appear. The electrocardiograph may enable us to make a diagnosis earlier in the course of the infection.

4. It was pointed out that one of the difficult problems of the physician in the treatment of children with chronic valvular disease is preventing the condition from progressing. It was suggested that the difficulty might in a measure be overcome by the education of the public, the early elimination of all possible oral and nasopharyngeal infections and the establishing of convalescent homes.

HYDROCHLORIC ACID MILK IN INFANT FEEDING *

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During the first year, the average normal infant exhibits, at the height of digestion, a range of gastric acidity (Kronenberg,[1] Marriott [2]) that lies between p_H 3.5 and 5.0. Between this and the range of acidity required for the action of the gastric enzymes, as determined in vitro, there is an interesting relationship, of much significance in the physiology of infant digestion. Chart 1 presents graphically the facts discussed in a previous communication.[3] Rennet, acting best between p_H 6.3 and 6.0, curdles milk soon after ingestion, before the height of gastric acidity has been attained. Chymosin (van Dam), an enzyme with feeble proteolytic powers, about which little is known, acts best at p_H 5.0. Gastric lipase and invertase (the latter studied, however, from yeast) are half active at about p_H 6.0, and fully active between p_H 4.5 and 4.0. Pepsin requires a much higher acidity, beginning to act at p_H 5.0, and developing half activity at about p_H 4.0 and full activity only at p_H 2.3, a point rarely if ever reached in the infant's stomach. It is clear that the stomach cannot perform its task in the digestive process without producing enough hydrochloric acid to raise the level of acidity to a point where the various enzymes will be activated. While this point varies for the different enzymes, we may for practical purposes assume a threshold of about p_H 5.0 as that which the gastric acidity must reach before any of them, excepting rennet, becomes usefully active. Milk, the chief food of infancy, offers a marked resistance to this necessary change in reaction because of its content of buffer substances,[4] which is particularly high in the case of cow's milk. To 100 c.c. of human milk, the equivalent of from 15 to 20 c.c. of tenth normal acid must be added before the threshold acidity of p_H 5.0 is reached, while to the same quantity of cow's milk, from 50 to 60 c.c. must be added (Chart 2).

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* Received for publication, Aug. 14, 1923.

* Read before the American Pediatric Society, May 31, 1923.

* From the Division of Pediatrics, Stanford University Medical School.

[1] Kronenberg, R.: Acidität und Pepsinverdauung im Säuglingsmagen, Jahrb. f. Kinderh. **82**:401 (Nov.) 1915.

[2] Marriott, W. McK.; Davidson, L. T., and Harshman, L. P.: Studies on the Digestion in Infancy. I. Hydrogen-Ion Concentration of the Gastric Contents, Tr. Am. Pediat. Soc. **34**:39, 1922.

[3] Faber, H. K., and Hadden, F.: The Influence of the Hydrogen-Ion Concentration and Buffer Value of Foods on Digestion, with Special Reference to Infancy, M. Clinics N. America **6**:245 (Sept.) 1922.

[4] Clark, W. M.: The Reaction of Cow's Milk Modified for Infant Feeding, J. M. Res. **31**:431, 1914.

Reduction of buffers, the prime essential of cow's milk modification for infant feeding, in the past has been effected in two ways chiefly, by dilution and by the use of bacterially soured milk. The former, because of the accompanying reduction of food value, has to be supplemented by the addition of unbuffered food stuff, such as carbohydrate.

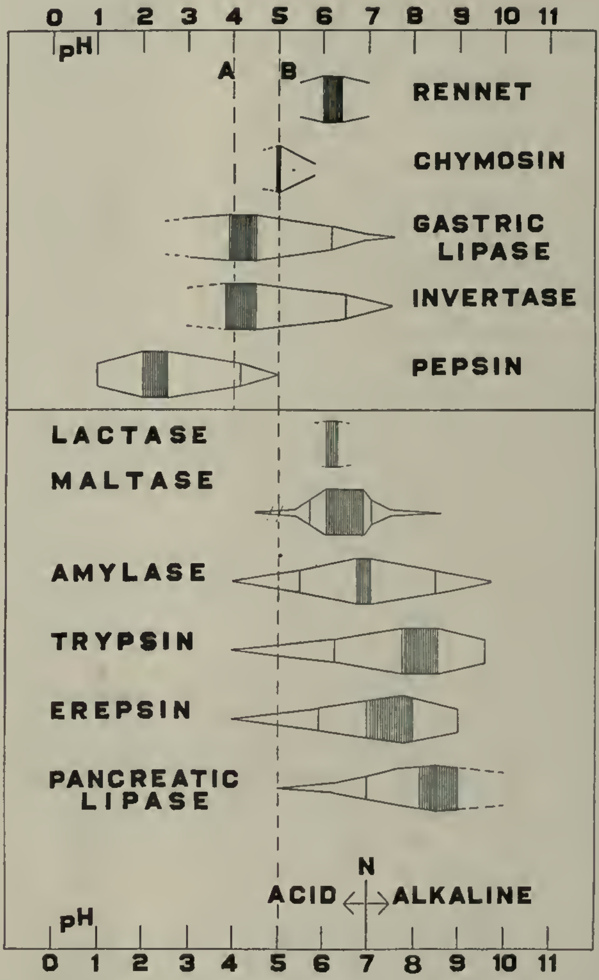

Chart 1.—Ranges of hydrogen-ion concentration within which the digestive enzymes act. The gastric enzymes are shown above, the intestinal (including the pancreatic) below. The individual graphs are intended to represent roughly the proportionate activity at a given p_H; the shaded areas showing the optimal range; the short vertical intersections, the points of half activity, and the apices, the points at which activity begins or ceases. Between lines *A* and *B* is the approximate range of acidity found in the normal infant's stomach at the height of digestion. The optimal ranges for gastric enzymes, with the exception of rennet, lie to the left (more acid side) of the threshold, p_H 5.0, and those of the intestinal enzymes to the right. *N* marks the neutral point p_H 7.0.

Usually, such compensation is partial only, with the result that bottle-fed infants are made to ingest larger volumes than breast-fed infants, of food containing much lower percentages of fat. Hence, they lose certain benefits incidental to an adequate intake of milk fat, such as vitamins and substances necessary to normal stool formation, and are subject to the risks of high carbohydrate feeding. It is in overcoming the risks and damage of high carbohydrate feeding that the second method of buffer reduction, the use of soured milk, has been found to be of the greatest value. It is noteworthy that, on soured milk, infants with previously disturbed digestion are frequently able to take fat in much higher percentages than it is customarily given even to healthy infants fed on sweet milk. Sour milk, moreover, can often be taken with little or no dilution, so that a smaller volume suffices to meet the caloric requirements. Protein milk is, of course, a modification of sour milk and has not only a high protein percentage but also a relatively high percentage of fat.

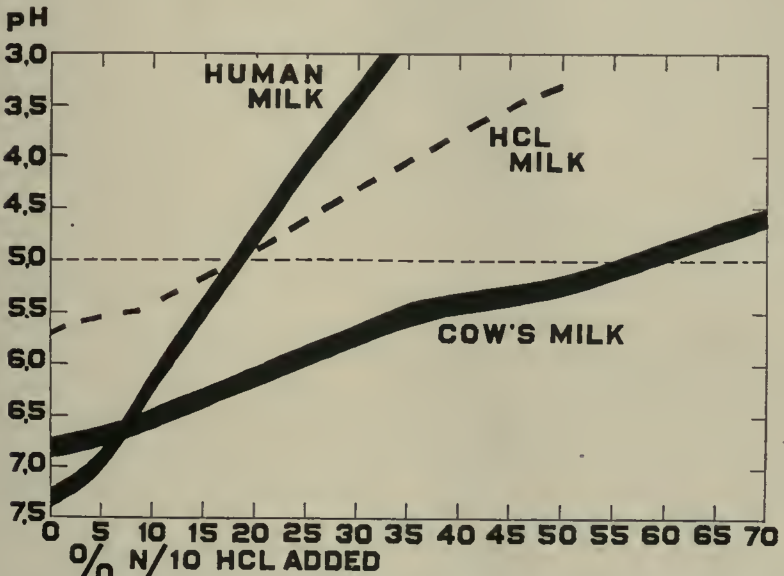

Chart 2.—Titration curves of human milk, cow's milk and 25 per cent. hydrochloric acid milk; ordinates, H-ion concentration in p_H; abscissas, percentages of tenth normal hydrochloric acid added. Human milk and hydrochloric acid milk curves intersect at about p_H 5.0 (dotted line), the acid level at which gastric digestion begins to be effective, showing that the buffer values to this level are similar. Some difference in buffer values to higher levels of acidity remains.

The effects of protein milk are characteristic and suggestive. Diarrhea ceases, usually within forty-eight hours, with a striking change in the stools, which become grayish, and pasty in consistency, being composed largely of calcium soaps. These effects have been commonly ascribed to the reduction in sugar (which fails to explain them), but the stools themselves certainly suggest as the outstanding effect an increase in lipolysis, and the reaction of the milk (p_H 5.5-5.0) strongly suggests that lipolysis in an acid medium, i. e., in the stomach, has been favored. One is led to consider the possibility that the use of sour milk is beneficial because it increases the activity and availibility of gastric lipase, initiating at an earlier period the difficult process of fat splitting, increasing the amount split in the stomach (where perhaps, in the presence of increased soluble calcium salts, calcium soaps are more readily formed, to appear eventually as the basis for the characteristic stools), and thereby promoting the completion of the task by pancreatic lipase in the intestine.

This function of the stomach has not received the amount of attention which it appears to deserve. Lipase was demonstrated in the stomach of infants by Sedgwick,[5] who believed that as much as 20 per cent. of the ingested fat may be split by it, and was further studied by Davidsohn,[6] who determined the range of H-ion concentration within which it acts and conclusively demonstrated its identity as distinguished from pancreatic lipase.

The success of protein milk therapy and of lactic acid milk feeding in cases of lowered digestive powers (Marriott[7]) raises the question as to whether there is to be found here some general principle of infant feeding, for which an easier, more accurate and more flexible technic could be devised, which would permit the feeding of higher percentages of fat and lower percentages of carbohydrate either in health or in disease. If an acid reaction and low buffer value in the food are favorable to the digestion of fats, it would seem reasonable to prefer a method which would give constant or known degrees of acidity and buffer value, and which would consume little time and be simple enough for use in the home, if necessary. There is considerable objection to bacterially soured milk. Marked variations in acidity occur in it according to the time and temperature of incubation, kind, freshness and quantity of culture used. It requires about twenty-four hours for preparation and numerous precautions must be taken. When bought in the market, it is expensive and variable in composition. Its usual acidity (p_H 4.0-4.5) is probably, for reasons to be discussed, not optimal for infant feeding, and gives it a sourness of taste which not infrequently causes infants to reject it for a considerable time.

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[5] Sedgwick, J. P.: Die Fettspaltung im Magen des Säuglings, Jahrb. f. Kinderh. **64:**194, 1906.

[6] Davidsohn, H.: Beitrag zur Magenverdauung des Säuglings, Ztschr. f. Kinderh. **9:**470, 1913.

[7] Marriott, W. McK.: The Artificial Feeding of Athreptic Infants, J. A. M. A. **73:**1173 (Oct. 18) 1919.

Theoretically at least, there seems to be no good reason why milk should not be soured for infant feeding by the addition of acid. Scheer,[8] indeed, has used a milk soured with hydrochloric acid in the treatment of tetany, though he has not advocated its use along the lines here discussed. In the present study, the reaction and buffer value of cow's milk have been modified for purposes of infant feeding by the addition of tenth normal (about 0.4 per cent.) hydrochloric acid. Two principles, governing the proportion of acid to milk, have been successively tried by actual experiment. The first, depending on the addition of enough acid to bring the reaction to the assumed threshold value, p_H 5.0—approximately 50 c.c. to each hundred cubic centimeters of milk—was found to have certain practical disadvantages, such as a rather sour taste, heavy flocculation of casein, refusal by some infants and failure (in one instance) to evoke the desired changes in the stools. The second principle, that of reducing the buffer value approximately to that of human milk, was found to give satisfactory results and has been employed throughout most of the later part of the experiment, and up to the present, with some exceptions in individual cases. For this modification, 25 c.c. of acid is added to each hundred cubic centimeters of milk, and the product called, for short, 25 per cent. hydrochloric acid milk (Chart 2). It is believed that milk thus modified is more nearly physiologic than that with more acid, since it demands from the stomach about the same secretory task (for acid) as does the natural food, breast milk.

TABLE 1.—*Changes in Cow's Milk Caused by Different Amounts of Acid*

N/10 HCl per Vol. Milk, per Cent.	p_H (Approx.)	Precipitate	Taste
0	6.9	0	
25	6.0	0	Not perceptibly sour
30	5.8	0	Just perceptibly sour
35	5.7	Slight	Slightly sour
40	5.6	Present	Slightly more sour
45	5.5	Marked	Moderately sour

Table 1 shows the changes in cow's milk caused by different amounts of acid.

The 25 per cent. hydrochloric acid milk, with its reaction of p_H 6.0, too slightly acid to alter the taste perceptibly, is taken by infants without protest. The acid is taken up largely by the basic phosphates which are converted in part into the more soluble acid phosphates and corresponding chlorids. The increase in soluble calcium salts may be an additional factor of advantage. No "free" acid is present in the milk.

The addition of hydrochloric acid to milk inhibits the growth of bacteria to some extent, improving the keeping properties.

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8. Scheer, K.: Die Beeinflussbarkeit der Spasmophilie durch Salzsäuremilch, Jahrb. f. Kinderh. **97**:130 (Feb.) 1922.

CLINICAL RESULTS

The most striking and characteristic effect of hydrochloric acid milk feeding, as of protein milk feeding, is the appearance, usually within twenty-four or forty-eight hours, of smooth grayish stools, consisting chiefly of calcium soaps. Soap stools have almost invariably occurred in the present series of cases, to this extent at least bearing out the theory of increased lipolysis. In spite of the appearance of soaps, in some cases the stools have remained rather loose, owing to the continued addition of sugar to the formulas. Experience has made it clear, as no doubt we should have anticipated, that acid does not facilitate the digestion of sugars, or at least does not obviate their ill effects once intolerance is established. This apparently holds even for cane sugar. On the other hand, experience has indicated quite definitely that acid added to milk affects very favorably the tolerance to fats, even when they have previously been ill borne. Vomiting has ceased, and curdy or greasy, mucous stools have given place to smooth, well-digested, neutral or alkaline stools. In two instances, the p_H of the stools was, respectively, 7.0 and 7.3. Sugar diarrhea, with watery, acid stools, and scalding of the buttocks, has yielded promptly to hydrochloric acid milk, normal soap stools occurring in nearly all cases within forty-eight hours.

Fairly high fat percentages are necessary, as with protein milk, to produce good soap stools. Beginning usually with a two-thirds whole milk formula, in most cases, we use top 5 per cent. and top 6 per cent. milk as a basis within a few days. In one instance, an error in instructions to a mother led to the administration, without any ill effects, of a formula containing nearly 8 per cent. fat.

That the beneficial effects obtained have been due directly to the acid has been shown in several cases in which attempts to withdraw the acid were promptly followed by a return of symptoms. In some instances, it has been possible to withdraw the acid within a comparatively short period, but in a number it has had to be continued for a period of months. No apparent harm has resulted from this.

Milk modified with hydrochloric acid has been used altogether in about thirty cases, but only in the last twenty has a fairly uniform technic (25 per cent. hydrochloric milk) been employed. The series is therefore not large enough to justify more than tentative conclusions. The results have, however, been uniform enough in certain respects to give definite promise of practical usefulness to the method. It appears to have value in the treatment of diarrheas when the sugars are at fault; in the treatment of the common fat intolerance of infancy; in cases in which we desire to increase the caloric intake without increase in the carbohydrate or undue increase in the volume; in cases in which, for any reason, we wish to increase the intake of fats, and, quite possibly, in the feeding of normal infants whenever cow's milk has to be used. In several cases of eczema, we have, without harm, and perhaps with some benefit, given much higher percentages of fat than are customary in this disease. It is possible, though we have not as yet had an opportunity to try it, that it may be useful in celiac disease.

While acid has not appeared to improve the digestion of sugar, it has not, apparently, rendered it more difficult; and in most instances, it has been possible, after a suitable interval, to introduce sugar again into the formula after full recovery from the original disturbance. It has, however, been possible to obtain good gains in weight without addition of sugar, or with the addition of very small amounts, by virtue of the increased fat intake. In all, we have had about ten cases in which diarrheas traceable to sugar have been cured by hydrochloric acid milk. In one instance, twins fed on the same formula throughout both showed a prompt cessation of the disorder when fed on top milk with hydrochloric acid and have both gained and developed normally over a period of three months since their recovery.

Two cases may be selected for detailed description.

REPORT OF CASES

Case 1.—Baby K., aged 6½ months, admitted April 9, 1923, had from fifteen to twenty green watery stools daily, accompanied by fever and scanty urination. The ears were discharging also, and the infant had suffered from otitis media since about March 20. The ears were opened, March 23, and had been discharging ever since. Diarrhea began about March 26 and had been more severe for the past three or four days. The formula employed contained 3.2 per cent. fat, 8.3 per cent. sugar and 2.5 per cent. protein. The physical examination was negative, except for the purulent discharge from the ears, and enlarged tonsils and adenoids.

Table 2.—*Formulas and Progress (Case 1)*

Date	Fat	Sugar	Protein	HCl, per Cent.	Remarks
4/ 9/23	4.8	4.0	2.4	14	Stools reduced to 5 or 6; still loose but containing soaps
4/12/23	2.8	3.5	2.1	25	More solid substance, less watery; still loose; has gained 130 gm.
4/16/23	2.9	3.6	2.2	29	About the same; lost 150 gm.; 4 or 5 stools a day
4/20/23	4.4	3.7	2.2	29	Stools, 1 to 3 daily; gained 190 gm. in 3 days; normal, well digested soap stools
4/27/23	4.4	5.0	2.2	15	Cane sugar added; stools continue good
4/28/23	4.4	6.3	2.2	15	Cane sugar increased; stools continue good, 1 or 2 daily; steady gain

Table 2 gives the formulas and progress from April 9 to 28.

April 29: The patient was discharged from hospital.

May 5: The patient was having two good stools daily. A good gain had been made. The hydrochloric acid was reduced to 8 per cent., because of expense. There was no other change. The baby had gained 4 ounces (113.4 gm.) in six days.

May 9: The patient had seven stools after the change in formula. The stools were fewer when the sugar was reduced. There had been a gain of 3 ounces (85 gm.) in four days.

Summary.—This patient was put on top milk to maintain calories in the presence of sugar intolerance. The immediate effect was to reduce the number of stools from fifteen to twenty to five or six. From being green and watery, they became soft, with fair amounts of soaps, but still rather loose. Marked improvement began after the percentage of hydrochloric acid was increased to 29 per cent. and the fats raised from 2.9 to 4.4 per cent. Reduction of the acid below 15 per cent later caused a temporary recurrence of diarrhea.

Case 2.—Baby B., aged 2½ months, admitted Feb. 17, 1923, had severe, forcible vomiting, dating from birth. The baby was breast fed until two weeks previously, and was weaned because the mother had influenza. The formula contained 10 ounces of milk, 12 ounces of water and some cane sugar. Vomiting usually occurred about fifteen minutes after feeding. There were one or two fairly good stools daily. The physical examination was essentially negative. No waves of pyloric stenosis were detected.

Table 3 gives the formulas and progress from February 17 to 28.

Table 3.—*Formulas and Progress (Case 2)*

Date	Fat	Sugar	Protein	HCl, per Cent.	Remarks
2/17/23	0.5	10.0	1.4	0	Slight regurgitation; 2 good stools
2/18/23	1.8	9.4	1.4	0	Three good stools
2/19/23	2.0	8.7	1.5	0	Losing weight; 3 or 4 poor stools containing curds and mucus
2/23/23	2.0	8.0	1.5	0	Has made one good gain; stools still poor, as before
2/24/23	2.0	8.0	1.5	22	Stools showed very marked improvement the morning of February 26 (stools of February 25), still containing fat curds but no mucus; curds nearly gone February 27, and none seen February 28; typical soap stools, smooth and well digested
2/28/23	2.0	7.5	1.5	20	Stools, 2 to 4 daily; steady gain; stools somewhat looser March 2; changed from cane sugar to Karo, and baby dismissed in good condition

Visits to the clinic were made March 15 and 28 and May 7. There was a steady gain, with an average of one stool daily, soft, yellow and normal. The infant was still taking hydrochloric acid. There had been a gain of 61 ounces (1,729 gm.) in the seven weeks since discharge.

Summary.—The fat intolerance was corrected by skimmed milk but with loss of weight. On hydrochloric acid, the infant was able to take fat in percentages previously ill borne, and to gain weight.

TRANSITION TO UNSOURED MILK

One of the troubles associated with bacterially soured milk and particularly with protein milk has been the difficulty in returning to unsoured milk. It can be done by adding increasing proportions of unsoured milk to the sour, a cumbersome and inaccurate process that is rarely if ever employed. With hydrochloric acid, the transition can be very accurately and easily made, merely by reducing the quantity of added acid at a rate graduated according to the patient's clinical response. We have in several cases been able to return to unsoured milk without difficulty. In some cases, in which the too rapid reduction was not well tolerated, it has been a simple matter again to increase the acid, and then reduce it more slowly, a process virtually impossible with bacterially soured milk.

CONTRAINDICATIONS

During the first month or six weeks of life, as is well known, protein milk and lactic acid milk are not as a rule well borne. We have repeatedly found the reaction of colostrum (the first ten days) to be fairly alkaline, p_H 7.7. The stomach of the new-born infant holds about 1 ounce, and it is estimated that with an intake of 3 ounces, two thirds of the milk has gone into the intestine by the time feeding is completed and before much change of reaction can have been produced in it by the gastric secretion. These facts appear to indicate that, in very young infants, proportionally much less digestion is gastric and more intestinal, the latter being optimal in an alkaline reaction (Chart 1). This may well point to the desirability of increasing the alkalinity of artificial food during the first month, lowering the buffer resistance to alkaline change, and may offer an explanation for the occasional usefulness of lime water. In any case, we have set a limit of 6 weeks of age as the earliest time at which acidified milk should be used.

CONCLUSION

This paper is intended to point out the usefulness of the acid modification of milk rather than to stress the value of a particular acid. It may be that hydrochloric acid may possess certain disadvantages, as yet undetermined, and that organic acids which burn to carbon dioxid will turn out to be preferable. Hydrochloric acid was selected largely because it is the physiologic acid. It is also cheap, easily standardized and everywhere available. We have made up samples of artificial lactic acid milk which are as palatable as hydrochloric acid milk, in the corresponding strengths, but have not as yet given them clinical trial.

SUMMARY

1. The excess of buffers in cow's milk delays, and in many cases prevents, the completion of gastric digestion in infancy by inhibiting the acidity necessary to the optimum efficiency of the gastric enzymes. Particular emphasis is laid on the importance of gastric lipase.

2. The principle that acidified milk favors the splitting of fats in the stomach may be used in the treatment of various disorders of digestion, particularly in fat and in sugar intolerance. In the latter case an increased digestion of fats appears largely to compensate for the necessary reduction in sugars.

3. In general, buffer reduction by acid has definite advantages over reduction by dilution, and may well be used in the feeding of normal infants.

4. Cow's milk to which one-fourth the volume of tenth normal hydrochloric acid has been added has been used in the majority of cases in the present series. Its taste and appearance are not perceptibly different from untreated milk. Its buffer value resembles that of human milk. Lime soap stools, like those from protein milk, occur when hydrochloric acid milk is fed.

5. Milk modified by the addition of acid has advantages over bacterially soured milk of convenience in preparation and ease of the graduated return to unsoured milk.

6. There are several reasons why acidified milk should not be used in very early infancy.

NEOPLASMS OF THE MEDIASTINUM IN INFANCY AND CHILDHOOD

REPORT OF A CASE OF GANGLIONEUROMA OF THE MEDIASTINUM IN A GIRL OF EIGHT YEARS *

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Although new growths of the mediastinum are very rare in childhood, the possibility of their occurrence should be bone in mind in the differential diagnosis of obscure intrathoracic conditions. The finding, on operation, of a large tumor mass in this region, in a child of 8 years, which had escaped recognition for more than a year, though studied very carefully, clinically as well as roentgenologically, prompted me to review the subject and present a study of the case.

The literature contains many articles on mediastinal neoplasms in general, without special reference to the young. Hare[1] presented a complete review of this subject, including patients of all ages. There have been, however, only a few studies of this condition in childhood by foreign writers, notably Schubert,[2] Rosenberg,[3] Bollog,[4] and Keating.[5] Up to the present time, as far as can be ascertained from a search of the literature, thirty-eight cases of mediastinal new growths in infancy and childhood have been described.

The clinical picture of neoplasms of the mediastinum is produced for the most part by compression of one or more of the structures lying in it. It is of considerable importance in diagnosis to associate the symptoms in an individual case with the organs involved.

Pressure on the trachea may cause a persistent cough, dyspnea, cyanosis and stridor; on the bronchi, cough and physical signs of decreased aeration to the corresponding lung.

Pressure on the esophagus produces difficulty and pain in deglutition.

Symptoms referable to compression of the veins will depend on whether the superior vena cava, the vena azygos major or the inferior vena cava is involved. Pressure on the first may produce edema of the face, neck, upper part of the thorax and arms; dilatation of the super-

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* Received for publication, Aug. 29, 1923.

* From the pediatric service of Mount Sinai Hospital.

* Case presented before the pediatric section of the New York Academy of Medicine, May 11, 1922.

1. Hare: Mediastinal Disease, Fothergillian Essay, 1889.
2. Schubert: Ueber Mediastinal Tumoren bei Kindern, 1887.
3. Rosenberg: Inaug. Dissert., Gottingen, 1881.
4. Bollog: Ueber Mediast. Tumoren in Kindesalter, Brugg F. Wild & Co., 1887.
5. Keatings: Encyclopedia of Diseases of Children, 1889-1890.

ficial veins of the face, neck and upper part of the thorax; cyanosis of the face; exophthalmos with disturbance of vision; tinnitus with impaired hearing; headache, and dizziness. Pressure on the vena azygos major is marked by engorgement of the intercostal veins and hydrothorax of the right side, and at times by pericardial effusion. Compression of the inferior vena cava may produce edema; dilatation of the superficial veins of the lower extremities, and albuminuria.

Pressure exerted on the heart will cause displacement and may produce irregular heart action; pressure on the aorta and its branches, diminution or inequality of the radial pulses, precordial pains and pallor.

The nerves which may become involved by the pressure of the new growth are the vagus, the inferior laryngeal and the sympathetic nerves. Compression of the first produces irregularity of the heart action, with slowing, syncope, difficulty in deglutition and cough. Pressure on the inferior laryngeal, causing paralysis of the posterior cricoarytenoid muscles, gives rise to stridor, brassy cough and inspiratory dyspnea. Involvement of the sympathetic nerves may produce inequality of the pupils, as well as palpebral fissures, and an enophthalmos of the affected side.

The neoplasm may grow forward, producing an erosion of the sternum and costal cartilages, or it may extend backward to the vertebrae and spinal cord, giving rise to a paralysis of the lower extremities.

Among the thirty-eight cases of mediastinal neoplasms in childhood, the following types have been described: sarcoma, 15; carcinoma, 9; dermoid cyst, 6; lymphadenoma, 4; from thymus of unknown character, 2; lipoma, 1; ganglioneuroma, 1.

Sarcoma of the mediastinum in childhood arises most commonly from the thymus gland. In six of the fifteen cases, it was unquestionably the origin of the tumor; in two others, it was given as the probable starting point. In two cases, the new growth developed from mediastinal lymph glands. No definite statement regarding the exact origin of the tumor was made in five instances. All the tumors, with the exception of four, whose type was not mentioned, were lymphosarcomas. The youngest child in this group was 1 year, the oldest, 14 years. There were nine boys and five girls. In one case, the sex was not mentioned. Death usually occurred from pressure of the invading growth. Radium was employed in one instance. The child improved for a short time, but later developed metastases in the abdomen, and died of general weakness and prostration.

The diagnosis of carcinoma of the mediastinum was made in nine cases. There is, however, considerable doubt as to the correctness of the pathologic reports of some of the early cases. The distinction between lymphosarcoma and carcinoma was not made clear. In three cases, the tumor was reported as primary in the mediastinum. One growth originated in the breast. In five cases, no statement was made as to the primary seat. The youngest patient in this group was 8 months, and the oldest, 12 years. There were four boys and four girls. The sex was not mentioned in one case.

There have been a large number of dermoid cysts of the mediastinum reported in the literature, notably by Morris[6] and Christian.[7] The symptoms of these congenital tumors are not usually manifest until adult life, and the diagnosis is rarely made in childhood. In six cases, symptoms did arise before adolescence. The youngest patient (reported by Medoei) was an infant. The tumor was situated in the anterior mediastinum and perforated into a bronchus, with the expectoration of hairs and cholesterin. The oldest child in this group was 12 years. In this case, a dermoid cyst was successfully removed from the mediastinum. In two cases death occurred from pneumonia.

Lymphadenomas have been reported in four cases, all in boys. The tumors arose in two cases from the mediastinal lymph glands, in one case from the thymus. No statement was made as to the origin of the tumor in the fourth child. The youngest was 6 years, the oldest, 12 years.

In two instances, cases of mediastinal neoplasm arising from the thymus were reported, but with no definite statement as to their pathology. Both children, aged 5 and 13 years, died of asphyxia.

One case of lipoma of the anterior mediastinum in a child of 1 year has been described.

The following case, observed at Mount Sinai Hospital, presented an unusual type of mediastinal neoplasm:

REPORT OF CASE

History.—I. B., a girl, aged 8 years, applied at the outpatient department in January, 1922, for relief of a persistent cough which had begun one year previously. The family history was negative. The birth was normal. The patient had had measles at 18 months, and whooping cough at 6 years. There were no other illnesses in the past. In addition to the harassing cough for a year, she suffered from slight dyspnea, progressive weakness and loss of weight. She had occasional attacks of vomiting, and at times short periods of irregular fever. There were no night sweats. She had been in another institution for the same condition four months previously.

Physical Examination.—The patient was undernourished, weighing 39 pounds (17.7 kg.). She appeared somewhat pale and moderately dyspneic. Examination of the chest revealed flatness on percussion over the entire right side. On auscultation over this area, there was markedly diminished vesicular breathing, except posteriorly at the angle of the scapula, where there was distant

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[6] Morris: Med. News, Sept. 16, 1905.

[7] Christian: J. Med. Res. **7,** 1902.

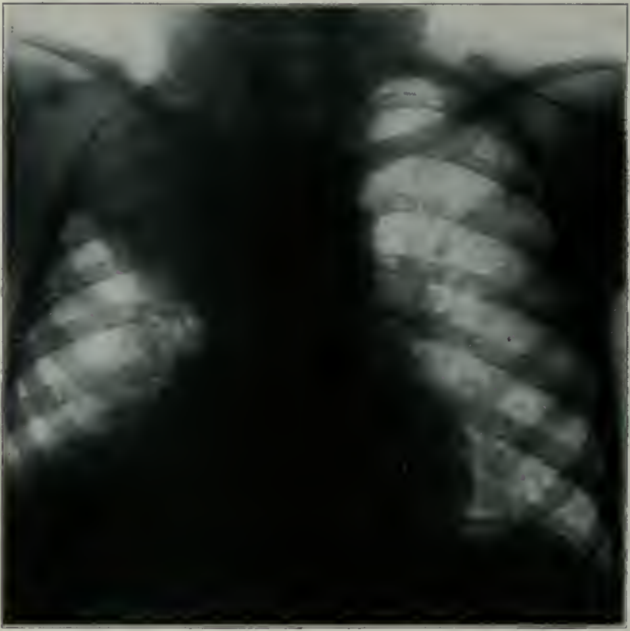

Fig. 1.—Ganglioneuroma of the mediastinum in a girl of 8 years.

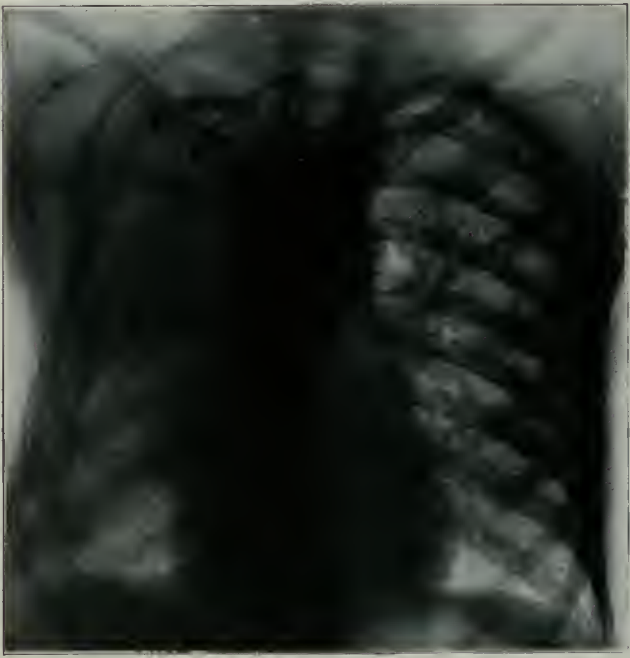

Fig. 2.—Appearance of chest after removal of the neoplasm. The drainage tube is still in place.

bronchial breathing. Fremitus was absent. The left side of the chest was normal. The heart was displaced very slightly to the left. The sounds were of good quality. There were no murmurs. The rest of the physical examination was negative. The urine was normal. Pirquet and Wassermann tests were negative.

Laboratory Findings.—Blood count revealed: 11,500 leukocytes; polymorphonuclears, 90 per cent.; lymphocytes, 10 per cent.; hemoglobin, 70 per cent.; erythrocytes, 4,200,000. Roentgen-ray examination of the chest (Fig. 1) revealed a large sharply defined shadow which occupied the region of the right upper lobe, extending to the third rib anteriorly. This was interpreted as an encapsulated effusion. At the right base, there was a less dense shadow, interpreted as an unresolved pneumonia.

The patient was admitted to the hospital service for further study. On aspiration of the right upper chest, 2 c.c. of bloody fluid was obtained. Culture of this fluid proved sterile.

Operation.—The child was then transferred to the surgical service, and Dr. Howard Lilienthal operated. He made an extrapleural approach through an incision posteriorly over the right upper lobe in the region of the sixth and seventh ribs near the spine. A large tumor mass, about the size of a tennis ball, was seen in the posterior mediastinum. A portion of the tumor was removed at this time. A week later, through the same wound, the rest of the mass was completely excised.

Roentgen-ray examination after the operation showed that the tumor had been entirely removed (Fig. 2).

Pathologic Report.—Dr. F. S. Mandlebaum reported the growth a ganglioneuroma. A photomicrograph of the neoplasm (Fig. 3) is shown through the courtesy of Dr. F. S. Mandlebaum.

Outcome.—Since the operation, the child's general condition has improved. The cough has markedly diminished and she has gained about 5 pounds (2.27 kg.) in weight.

While the patient was on the ward, some eye manifestations were noted by the ophthalmologist, Dr. J. Wolff. The right palpebral fissure was smaller than the left; the right pupil was smaller than the left, and there was an enophthalmos of the right eye. This syndrome is due to an involvement of the sympathetic nerve.

A ganglioneuroma is a neoplasm composed of ganglionic cells and nerve fibers. It usually originates in the sympathetic system. It is commonly benign, but malignant cases have been described. A considerable number of cases have developed in the suprarenal body. The abdominal segment of the sympathetic nerve has been the most common seat of origin. Loretz[8] described the first case of ganglioneuroma of the mediastinum in a man of 33 years. Later, Borst,[9] Rindfleisch,[10] Tschistowitsch[11] and Friedrich[12] described other cases, arising from the thoracic segment of the sympathetic nerve. All of these cases were in adults.

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[8] Loretz: Virchow's Arch., 1905.

[9] Borst: Die Lehre von den Geschwulsten, Wiesbaden, 1902.

[10] Rindfleisch: Text Book of Pathol. Histology, 1872, translated by William Kloman.

[11] Tschistowitsch, cited by Pick and Bielschowsky: Ztschr. f. ges. Neurol. u. Psychiat., 1911.

[12] Friedrich: Frankfurter Ztschr. f. Path., 1911.

Dunn[13] has reviewed the literature completely up to 1915 and found records of fifty-one cases of ganglioneuroma. Among these patients, there were seventeen children. In none of the cases occurring in children was the mediastinum or thorax involved.

The only other case of ganglioneuroma of the mediastinum in childhood was described by A. P. Stout.

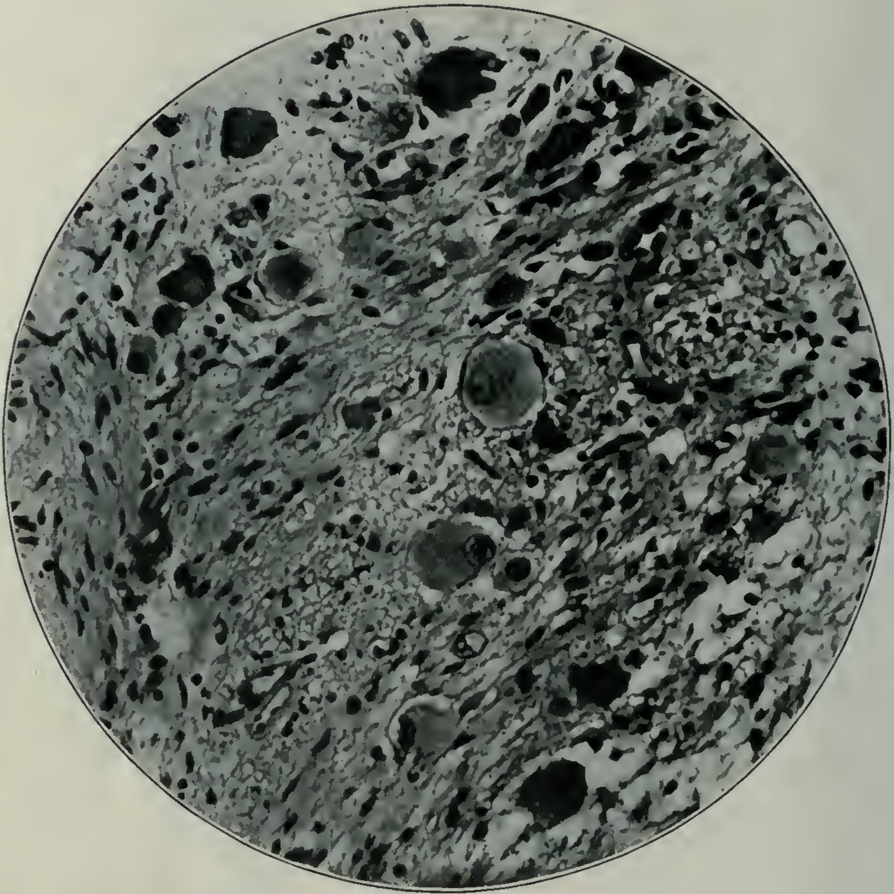

Fig. 3.—Photomicrograph of ganglioneuroma, showing ganglionic cells and nerve fibers.

In a child of 2½ years, there was a history of gastric disturbances for seven months, and weakness of the lower extremities for four months. Physical examination revealed signs of pressure on the spinal cord in the thoracic region. Roentgen-ray examination revealed a large mass in the upper portion of the left thoracic cavity. For a time, the case was regarded as an inoperable sarcoma. Subsequently, however, the child was operated on in the Neurological Institute for the relief of pressure on the cord. A large tumor which had extended from the thorax was found in the spinal canal. The child died soon after the operation. Microscopic section of the tumor showed it to be a ganglioneuroma.

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[13] Dunn: J. Path. & Bacteriol. **19,** 1915.

In our case, there was no extension of the tumor beyond the thorax; nor were there any metastases. The complete extirpation of the ganglioneuroma will undoubtedly insure a permanent cure.

The subject of mediastinal neoplasms in childhood was reviewed to emphasize the importance of considering this condition in the differential diagnosis of intrathoracic disease. A case of ganglioneuroma of the mediastinum was reported because of its great rarity and to show the possibility of the successful operative removal of the growth.

CHRONIC ULCERATIVE COLITIS IN CHILDHOOD *

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A careful search of the literature has failed to reveal a single article dealing with chronic ulcerative colitis in childhood. Of the five cases to be considered in this paper, four were observed in the last two years, and one was reported by Logan[1] in 1919. Although different in their mode of onset, when fully developed these cases appear to be the same, the chronic recurring dysentery with watery, bloody passages, marked emaciation, persistence of the symptoms in spite of treatment, and the absence of any known etiologic factor, such as *Bacillus dysenteriae,* ameba, *Balantidium coli,* or tuberculosis making a definite clinical entity.

Chronic ulcerative colitis, as defined by Logan, is a chronic inflammation of the large bowel, of unknown etiology, and showing all grades of inflammation, from a reddened, congested, easily bleeding mucous membrane, to superficial and deep ulceration, with constant or recurring dysentery, lasting from many months to several years.

Logan was the first, in this country, to report a large series of cases of chronic ulcerative colitis in adults. Since then, a considerable number of articles have appeared on the subject. The condition was described by White[2] in 1888, as a clinical entity. The anatomic changes had been described, no doubt, in the terminal stage, by Rokitansky,[3] Virchow[4] and others, as polyposis of the colon, the polypi being formed by a proliferation of the islands of mucosa remaining in the ulcerated colon. In order to convey an idea of the condition, it will be necessary to cite, in detail, the outstanding features of these five cases.

REPORT OF CASES

Case 1 (Reported by Logan).—*History.*—G. M. G., a boy, aged 10 years, was brought to the Mayo Clinic, June 26, 1907, because of bloody diarrhea. He had had whooping cough and measles, and at the age of 8 years, a spell of chills and fever resembling malaria. His subjective symptoms had begun about a year and a half before, with general abdominal pain, followed in a

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* Received for publication, Aug. 8, 1923.

* From the Section on Pediatrics, Mayo Clinic.

* Read before the American Pediatric Society, French Lick, Ind., May 31, 1923.

1. Logan, A. H.: Chronic Ulcerative Colitis: A Review of One Hundred and Seventeen Cases, Northwest Med. **18**:1-9 (Jan.) 1919.

2. White, W. H.: On Simple Ulcerative Colitis and Other Rare Intestinal Ulcers, Guy's Hosp. Rep. **45**:131-162, 1888.

3. Rokitansky, K.: A Manual of Pathologic Anatomy, 4 vol., London, Sydenham Society, 1849-1854.

4. Virchow, R. L. D.: Die krankhaften Geschwulste, 3 vol., Berlin, Hirschwald **1**, 1863.

few days by bloody diarrhea. He was in bed for two weeks, and his mother thought that the blood had been darker, and had been seen only occasionally in the mucus since that attack. He had had no night sweats, but occasionally there had been an afternoon rise in temperature. Recently, the stools had been copious, the movements usually being associated with slight pain.

Examination.—The child was rather pale, and had slight general abdominal tenderness. His temperature was 101 F. The hemoglobin was 50 per cent. Repeated stool examinations for tubercle bacilli and amebae were negative. Proctoscopic examination revealed a markedly congested mucous membrane, with a few small, rather shallow ulcers.

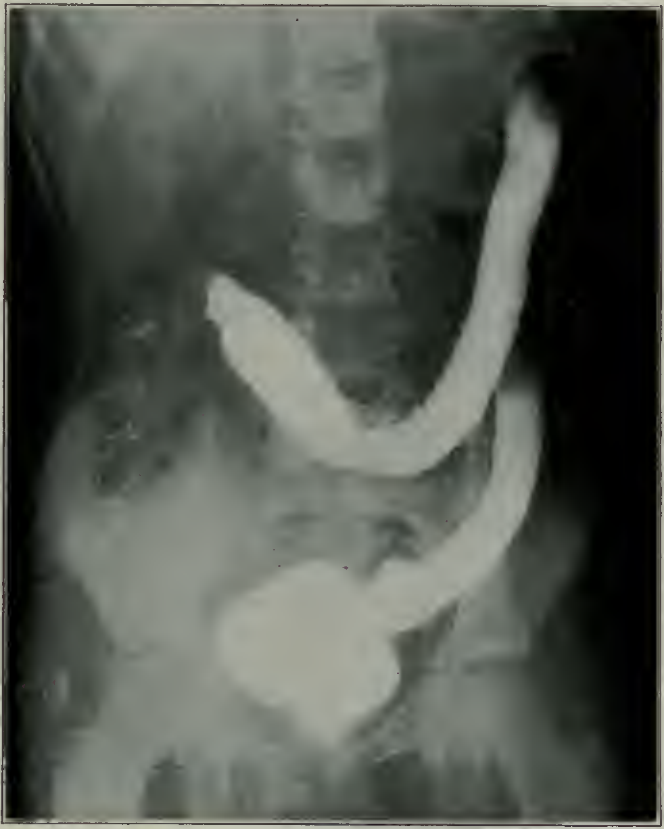

Fig. 1 (Case 1).—Roentgenogram of colon showing absence of haustrations.

Course.—The patient was not seen again for nine years, when he returned, complaining of thin, mucous stools with occasional clots of blood. He had been having from three to five stools daily, thin and watery, with flecks of blood and occasionally a large hemorrhage of bright blood. He had had slight attacks of colic, and had seemed to do better on a full diet than on a restricted one. He had been taking calomel every few days for several years. Examination of the stool did not reveal any parasites. Bismuth subcarbonate, one teaspoonful three times a day, was given. Two months later, there was some improvement. While the patient was under bismuth treatment, the stools decreased to about three a day. Roentgenograms at this time revealed a thickened, contracted colon without haustrations. One year later, the patient was still having from three to five movements a day, and was more relieved by taking bismuth than by any other mode of treatment.

CASE 2.—*History.*—M. H., a girl, aged 10 years, came to the Mayo Clinic, Jan. 19, 1922, because of bloody diarrhea. She had had measles, whooping cough, chickenpox, pneumonia, at the age of 2 years, and influenza at 6. The tonsils and adenoids had been removed at the age of 6 years. At the age of 2½ years, she had her first attack of bloody diarrhea. At this time, she was in the hospital for about three weeks, and gradually recovered. Six months later, she had a second attack, and this time remained in the hospital for one year. During most of this time, she had from eight to ten stools a day, and often passed large clots of blood. She was under the care of a number of physicians. At first she was on an oatmeal diet, and later on a buttermilk diet, which seemed to make the diarrhea worse. Without much change in diet, or any particular medication, she gradually improved and was able to take a general diet. For about seven years, she was fairly well. In the fall of 1921, she had a return of her old condition, with dysentery and a good deal of blood and mucus. There had been no irregularity of the diet, and a slight cold was the only premonitory symptom. During September, 1921, the stools were often as numerous as twenty-nine a day. At this time, the patient's home physician had under his care eight other cases of diarrhea, which ran the usual course, clearing up in the course of a few weeks. In the last two years, she had complained a good deal of headache, and abdominal pain in the region of the liver. Her general condition had gradually become worse. Her appetite was very poor. During the last three months, the stools had been less frequent, although there was considerable mucus. Recently, the stools had again increased to eight or ten daily, with passage of blood clots almost every day. The patient had considerable tenesmus and frequent cramplike pains in the abdomen, with the bowel movements.

Examination.—The child was markedly underweight, weighing only 49½ pounds (22.5 kg.). The hemoglobin was 60 per cent.; the erythrocytes numbered 3,900,000, leukocytes, 5,000, lymphocytes, 37 per cent., transitionals, 5 per cent., neutrophils, 45 per cent. and eosinophils, 6 per cent. The urinalysis and the Wassermann reaction were negative. Repeated Pirquet tests gave negative reactions. Roentgenograms of the chest revealed nothing abnormal. The roentgenogram of the colon was typical of chronic ulcerative colitis, showing a narrowed colon without haustrations (Fig. 1). An aphthous stomatitis was present. Proctoscopic examination revealed marked ulcerative proctitis with probable colitis. Examination of the stool was repeatedly negative for tubercle bacilli, amebae or other parasites. Cultures were negative for dysentery, typhoid or paratyphoid bacilli. The blood cultures were also repeatedly negative.

Treatment.—The patient was admitted to the hospital and put on a bland diet. In view of the possibility of amebic infection, she was given emetin hydrochlorid, 0.02 gm., twice a day for three days. Daily stool examinations were made for amebae, without success. Four days after the patient entered the hospital, acute arthritis of the left knee developed, followed in four days by an infection in the right knee. About the same time, slight stiffness of the neck also developed. Local irrigations with the usual antiseptics were without benefit. During all this time, the patient had an irregular fever of between 99 and 100 F., occasionally reaching 102 F. The fever seemed to be definitely associated with the arthritic symptoms, as with each new flare-up there was a corresponding rise in temperature.

Operation.—After one month of treatment and a gradual loss of strength and weight, it was decided to perform an appendicostomy. Because of the inflammatory condition of the appendix, however, this was impossible; instead, the appendix was removed and a cecostomy was made by suturing a catheter into the cecum at a point just above the stump of the appendix. The cecum, at the point where the cecostomy was made, was sutured to the peritoneum. After the operation, the temperature rose to 102 F. for three days, and then gradually subsided, and continued to range between 99 and 100 F.

Course.—The condition of the joints remained about the same, and there was slight stiffness and aching in the right hand and left foot. Two weeks after operation, irrigations through the cecostomy wound were begun, with hot saline solution, the solution being allowed to run in slowly enough not to cause pain. The patient could tolerate only small amounts of fluid. She left the hospital April 17, slightly improved, but there was still considerable pus in the stools. Although the arthritic symptoms were less marked, there was still considerable pain in both knees.

After the patient returned home, the saline irrigations were continued. Gradually, the blood disappeared, and finally the mucus in the stool. In August, 1922, although her physical condition had improved markedly, she was having from four to six movements in twenty-four hours, with occasionally a small amount of blood. She was still receiving a hot saline irrigation for one hour each day. The arthritis had completely cleared up.

The last report from the patient was received, March 11, 1923. Since Christmas, 1922, she had had one or two normal bowel movements a day. The blood had entirely disappeared from the stools, and the irrigations had been stopped. She had been gaining at the rate of about a pound a week for the last two months, and had recovered her good color.

Case 3.—*History.*—H. L., a girl, aged 11 years, came to the Mayo Clinic, Sept. 20, 1922, complaining of dysentery and loss of weight. She had had chickenpox, measles, mumps and whooping cough, and, at the age of 3 years, milk poisoning. The present illness began in December, 1921, when the mother noticed bloody stains on the underwear. She thought at first that the child was beginning to menstruate. She was taken to a physician and treated for an ulcer of the rectum for two weeks, without improvement. At this time, she developed acute bronchial pneumonia, which lasted for about ten days, and had a bad effect on the condition of the bowels. The stools became frequent, from ten to twelve movements a day, accompanied by enormous hemorrhages. High enemas were given. The child was confined to bed until March, 1922, because of the intestinal trouble. She received silver nitrate and starch enemas, also opiates and bismuth, without effect.

In March, she was taken away for consultation, and after three weeks of examination, the diagnosis of amebic dysentery was made, although so far as the mother knows, amebae had never been found. The child was treated with emetin and ipecac, and also with coal oil enemas. She received arsphenamin intravenously, and 30 grains (2 gm.) of quinin a day for three weeks. All food except a small amount of carbohydrates was withheld for fifteen days. During this period, she lost gradually in weight, weighing about 29 pounds (12.2 kg.) instead of her normal of 55 pounds (25 kg.). She was given a transfusion, and later put on a more liberal diet, when she gained in weight. In June, further cultures were taken. By agglutination, it was determined that she had an infection of the Flexner bacillus. Repeated doses of serum were given intravenously, once with marked anaphylactic shock, when artificial respiration was required to resuscitate her. She gained slightly, so that by September, 1922, her weight was 48 pounds (21.8 kg.). Since the serum had been administered, the mother thought that the movements had been more nearly normal, but the least increase in diet resulted in liquid movements.

Examination.—The child was markedly underweight, weighing 47.5 pounds (21.6 kg.), the normal weight for her height being 68 pounds (31 kg.). She was having about eight bowel movements a day, with blood and mucus. The hemoglobin was 42 per cent.; the erythrocytes numbered 4,260,000, and the leukocytes, 20,000. The Wassermann and Pirquet reactions were negative. Examinations of the stool were negative for dysentery, amebae and other intestinal parasites. Roentgenograms of the colon revealed a chronic ulcerative colitis, practically the entire large bowel being involved (Fig. 2). There was ulceration (2 +), as far as could be seen with the proctoscope, without much, if any, contraction of the bowel.

Operation.—In view of the marked involvement of the colon, the anemia and the marked loss in weight, it was decided not to attempt local treatment, but to perform an ileostomy immediately. The parents, before consenting to the operation, wished to consult their home physician, and the child, therefore, was given a transfusion, and was allowed to return home. She returned two weeks later, and a Brown operation was performed. She stood the operation well, but developed a slight infection around the ileostomy openings. Further transfusions were given, so that, November 11, the hemoglobin was 55 per cent.; the erythrocytes numbered 4,000,000, and leukocytes, 13,000.

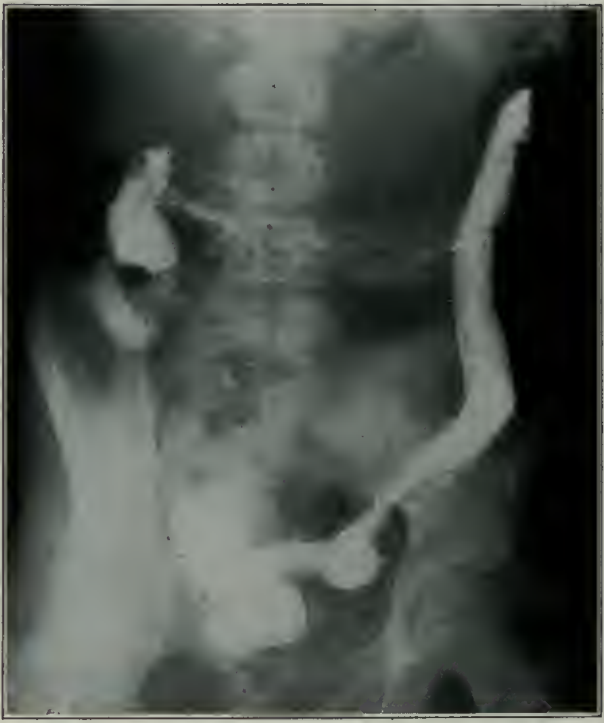

Fig. 2 (Case 3).—Roentgenogram of colon.

Course.—The patient was definitely gaining in strength, and the appetite was excellent. Hot saline irrigations through the lower ileostomy opening were started. November 11, the child was able to walk. Her main difficulty was excoriation around the wound, from the fecal material. No fecal material was passing through the rectum, and as a result of the daily saline irrigations, the secretion from the bowel became gradually free from blood, and finally just a little mucus passed several times a day from the large bowel. Following the irrigations, 1 ounce of 2 per cent. scarlet red in olive oil was injected into the lower bowel. November 30, the patient's weight was 46 pounds (21 kg.). On proctoscopic examination, December 5, the condition of ulceration was not much improved over the first examination. The degree of involvement was about 3, and the general appearance was not so angry. December 30, the weight was 50 pounds (22.7 kg.); January 30, 54 pounds (24.5 kg.), and February 5, 56 pounds (25.4 kg.).

On dismissal, February 6, the patient's general condition was markedly improved. She had regained her pink cheeks, and her arms and legs had filled out. There was still a small area of redness around the ileostomy opening. The stools were somewhat solid in consistency, although there was an occasional liquid stool. There was no discharge from the large bowel except on irrigation. No pus nor blood had been seen for the last month. Proctoscopic examination revealed decided improvement in the degree of ulceration. At no time during the patient's stay in the hospital did the temperature go above 100 F., and it was usually normal. She was sent home on a diet of milk, eggs, meat, bacon, cereal, orange and baked apple. The saline irrigations were to be continued once a day, 1 quart of saline being used, and irrigation being followed by injection of 1 per cent. scarlet red in olive oil.

A recent letter states that the child weighs 61 pounds (27.7 kg.); that the stools are formed for the most part, there being probably only one liquid stool in twenty-four hours, and that the skin condition about the wound appears to be very much better.

Case 4.—*History.*—G. L., a boy, aged 8 years, complaining of dysentery, was examined at the Mayo Clinic, Nov. 19, 1922. The patient had been well until March, 1921, when he had scarlet fever, complicated by otitis media. Following this, bloody and mucous stools were frequent for four months, when he was put in a hospital in Kansas City. At that time, the tonsils, adenoids and four carious teeth were removed, and circumcision was performed. These measures seemed to have a definite effect in decreasing the intestinal blood. The patient was placed on a more liberal diet, and he returned home greatly improved, although his father and mother believe that he was never completely free from dysentery, and the slightest indiscretion in diet would bring on a return of the diarrhea. He attended school regularly the following year, and seemed to be fairly well until August, 1922, when he developed an acute recurrence of the mucus and blood in the stools, associated with fever. One week later, there was a large hemorrhage of bright blood from the bowels. Three injections of serum for bacillary dysentery were given, without much improvement. In September, the boy developed, as a complication of the rectal ulcerations, a perirectal abscess, which had to be opened. A number of fistulas developed, leading to sloughing of the sphincter and loss of control. Then the dysentery gradually decreased until two weeks before examination, when the stools again became very frequent, containing much blood and mucus, and the boy lost ground very rapidly. The stool examination was negative for Flexner organisms and ameba, as were also the blood cultures. Barium sulphate injection and feeding seemed to point to an ulcerative involvement of the duodenum and entire colon. One week before examination, the boy had been given a second serum inoculation. For the last two weeks, he had taken practically nothing by mouth, and had lost 8 pounds (3.6 kg.) during this time.

Examination.—The boy was in an extremely serious condition, markedly emaciated, with a dry skin, sordes of the lip, impetiginous eruption over the body, deep ulcers in both cheeks and a large ulcer of the soft palate. Examination of the lungs and heart was negative. There were enormous fistulas around the rectum, with much sloughing and mucopurulent exudate around the anus.

Treatment.—The child was taken immediately to the hospital. Saline irrigations were used in the mouth every two hours, and the ulcerated areas were painted with 5 per cent. silver nitrate solution twice a day. On the day after admission, he developed extensive urticarial lesions over the entire body, probably due to the serum given the week before. Sitz baths were given for the local condition around the rectum. It was almost impossible to get the boy to take fluid. Besides the Sitz bath, light treatment was given locally to the buttocks. The urinalysis was negative. The hemoglobin was 61 per cent.; the erythrocytes numbered 3,044,000, and the leukocytes, 6,800. Repeated cultures of the stool for dysentery or typhoid, blood cultures, and examination of the stool for amebae or other parasites were negative. The temperature continued to range between 100 and 103 F.

Operation and Course.—Two weeks after admission, since no improvement was being effected under local treatment, it was decided to perform a cecostomy. Because of the very emaciated condition and the lowered resistance of the child, in spite of a transfusion previous to the operation and another afterward, he did badly and the wound showed little tendency to heal. There was a breaking down of tissue around the cecostomy opening, which was further complicated by the discharge of fecal material. In spite of a short circuiting of the feces, the infected area around the rectum showed no tendency to heal. All food had to be forced. Although there were temporary periods when the bowels seemed to tolerate a fair amount of food, each time that the amount was increased, there were enormous watery discharges through the cecostomy opening. The boy continued to lose weight, until he was nothing but skin and bones. Hemorrhages appeared everywhere, even on the slightest pressure of the skin. In spite of feeding with almost entirely protein food, the bowel movements could not be controlled, and the boy finally died from sepsis and starvation.

Necropsy.—The body was extremely emaciated (grade 4), and over the skin of the whole body were numerous, very irregular hemorrhages, 3 cm. or less in diameter, and small abrasions. The edges of the wound were edematous and congested, and covered with granulation tissue, and a slightly cloudy serous secretion exuded. The colon, 15 cm. above the cecum, was adherent to the wound in the skin, and opened into the wound. The colon and a part of the small intestine were taken out through the wound. There were a few fibrous adhesions of the peritoneum, most of which was, however, smooth and glistening. In the colon, and in the lower part of the small intestine, there were numerous, very irregularly formed ulcerated areas on the mucosa, of varying sizes, with only a scant deposit of fibrinous material on the floor of these ulcerated areas. The edges of the ulcerated areas were often undermined; the mucosa in such places was slightly thickened. In some areas, the muscular coats were ulcerated down to the peritoneum. The spleen was dry and firm; the lymphoid nodules were indistinct. The liver was firm, and the markings were distinct. Under the capsule, there were distinct regular cloudy spots (lobules). The cortex of the suprarenals was uniformly gray and cloudy. There was an autolytic softening of the medulla. The right psoas was partly destroyed, gangrenous, edematous and infiltrated, around an abscess leading up from the site of operation. In the upper part of the duodenum there was a scarlike surface, apparently an old healed ulcer. Arteriosclerosis of the aorta was evident.

Case 5.—*History.*—M. K., a girl, aged 15 years, came to the Mayo Clinic, Feb. 3, 1923, complaining of diarrhea with an acute onset a year and a half before. The patient had come to the clinic at the age of 8, because of repeated attacks of infection of the upper respiratory tract. At that time, the tonsils were removed. She had been well until the onset of diarrhea. In July, 1921, she and several other members of a camping party had had acute intestinal disturbances, which cleared up rapidly. The following September the patient had had a return of the diarrhea. There were a number of cases of diarrhea in the community at the same time, but in no other instance did the condition persist. After September, 1921, the patient had five or six movements daily, with a considerable amount of mucus, but no macroscopic blood, and little pain or other complaint. She was relieved temporarily when on a diet. For the last two months, she had had eight or nine thin, watery stools, with a slight amount of mucus, preceded by cramps and marked urgency. Medication gave only temporary and very slight relief. During the last year, the patient had lost about 5 pounds (2.27 kg.). She had experienced less inconvenience on a solid and semisolid diet than on liquids and a soft diet.

Examination.—The patient weighed 90 pounds (41 kg.), being almost 20 per cent. underweight. She was somewhat anemic and markedly emaciated. There was slight rigidity of the upper right and upper left rectus, but no pain or tenderness. There was slight edema of the lower limbs. The hemoglobin was 81 per cent.; the erythrocytes numbered 4,900,000, and the leukocytes 10,000. Urinalysis, and examination of the heart and lungs were negative. Roentgenograms of the colon revealed typical ulcerative colitis (Fig. 3). Examination of the stool was negative for parasites and ova, but positive for blood and pus. Stools were negative for tubercle bacilli on repeated examination. The proctoscopic examination of 15 cm. of the colon revealed ulcerative proctitis and granular ulcerations, with considerable blood, pus and mucus.

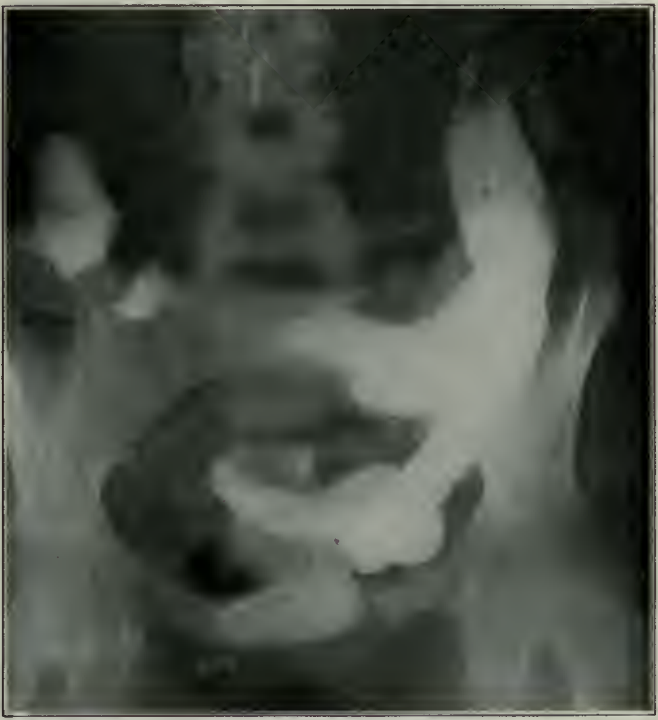

Fig. 3 (Case 5).—Roentgenogram of colon.

Operation and Course.—The patient was admitted to the hospital the following day, and because of her very weakened condition and the extensive involvement of the colon, it was decided to perform an appendicostomy rather than to risk an ileostomy. She seemed to do very well for a time after the appendicostomy. However, slight sloughing developed around the wound, gradually extended, and continued to spread in spite of light treatment. The patient's appetite was very poor, and she lost weight rapidly. April 12, numerous ulcers appeared on the buccal mucous membrane, and became very painful. A marked edema of the left lower extremity developed. In spite of every attempt to feed the patient, she continued to lose weight. She weighed at this time about

60 pounds (27.2 kg.). Even with continued irrigations, the condition of the bowel did not show any tendency to improve, and the patient died, April 19.

Necropsy.—Nine and two-tenths centimeters of the wound was unhealed. The skin of the wound was separated 5.5 cm. at its broadest diameter. The left thigh was considerably discolored, and somewhat larger than the right. The appendicostomy opened into the center of the unhealed area. There were numerous soft adhesions between the ileum and the anterior abdominal wall, particularly in the region of the operation. The diaphragm reached the fourth spaces on the right and left. Numerous soft adhesions were found at the apex of the pleural cavities anteriorly. Seven hundred and fifty cubic centimeters of dark brownish fluid was found in the right cavity. An ulceration in the esophagus, about 2 cm. in length, opened into the right pleural cavity. The pericardial cavity contained 15 c.c. of clear straw fluid. The heart muscle was pale, and the coronaries disclosed arteriosclerosis 1—. There were fine

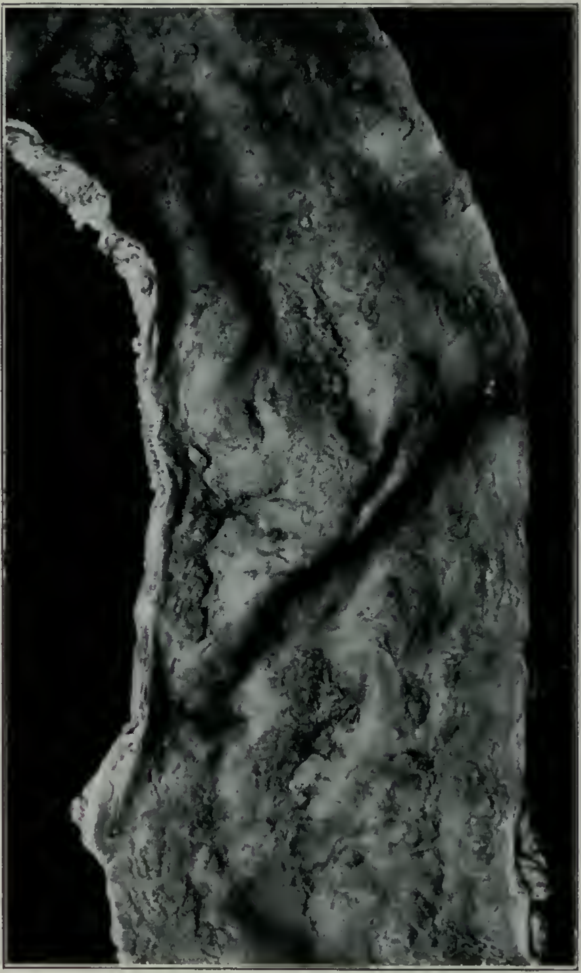

Fig. 4.—Section of colon showing multiple ulcers on mucosal surface.

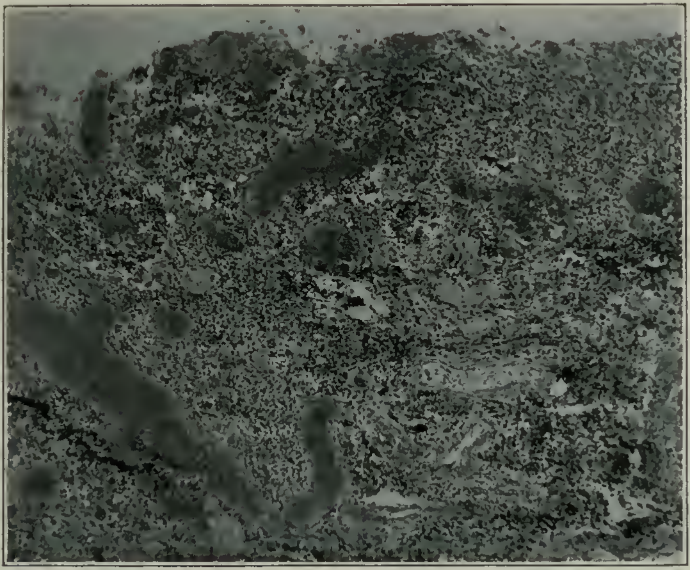

Fig. 5.—Changes on the submucosa.

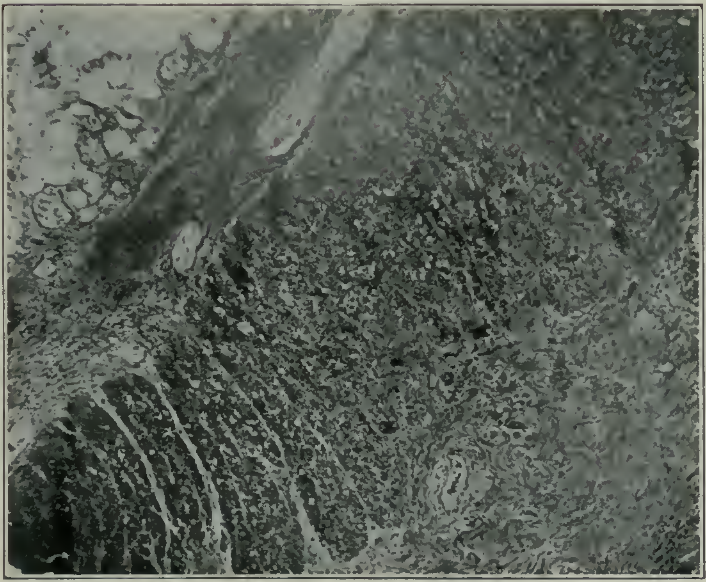

Fig. 6.—Degenerative changes in the inner muscular layer.

interlobar adhesions on the right side between the upper and middle lobes. The spleen, which weighed 60 gm., was soft, with indistinct corpuscles and fairly prominent trabeculae. The liver weighed 1,050 gm. The markings were indistinct, and numerous pale yellow areas, suggesting fatty change, were scattered throughout.

There were no gross lesions of the stomach or duodenum; throughout the colon, covering practically the entire mucosal surface, were multiple ulcers (Fig. 4). The remaining patches of mucosa were thickened, and appeared as islands in the ulcerated area. Numerous areas were ulcerated down to the serosa. The mucosa of the ileum was edematous and congested for a distance of about 60 cm. from the ileocecal valve, and numerous small ulcerations were scattered throughout this area. Three large ulcers, measuring approximately 3 cm. in diameter, were found in the rectum, and the remaining mucosa was extremely congested. The left iliac vein contained a thrombus, which extended up to the juncture with the inferior vena cava. The sections of the ulcers revealed extremely vascular bases, consisting largely of new connective tissue infiltrated with leukocytes. Numerous lymph vessels, filled completely with pus cells, were seen. Figure 5 shows the nature of the changes on the submucosa, and Figure 6, the degenerative changes in the inner muscular layer, consisting of edema, hemorrhage and breaking up of the fasciculi.

COMMENT

So far as is known, there is no single definite etiologic factor in chronic ulcerative colitis. The condition may be the result of a variety of infections, pyogenic, dysenteric, amebic or tuberculous; but wherever a specific cause can be demonstrated, the condition is usually not considered chronic ulcerative colitis. In none of the five reported cases were we able to demonstrate the presence of any of these infections. In only two instances (Cases 2 and 5) were there other cases of dysentery in the community, and in these two epidemics, all other patients recovered uneventfully in the course of a few weeks. In Case 4, the patient had his first attack following scarlet fever complicated by otitis media. In four of the five cases, the colitis started acutely with a bloody diarrhea. In only one instance (Case 3) was the condition chronic and without diarrhea. The onset was so lacking in symptoms that the small amount of bloody mucus which the mother noticed on the child's underclothing was interpreted as the beginning of menstruation. When it continued for a few weeks, however, medical advice was sought. In spite of treatment, the girl became gradually worse. Dysentery did not develop, however, until several weeks later, following an acute bronchopneumonia.

As is seen most definitely in Case 3, the ulceration begins in the lower portion of the bowel, and in the course of the illness the entire colon is involved. Only rarely is the ileum involved. In Cases 4 and 5, both of which came to necropsy, there were ulcerations in the ileum. In only one of Logan's 117 cases was there local involvement of the colon, which was not continuous with the process lower in the bowel. On proctoscopic examination, the ulcers are usually most marked in the rectum and lower sigmoid, and in the early cases become less numerous in the sigmoid. The colon is usually thickened, the surface appearing red and glazed, with numerous small ulcers. In the severe cases, only small islands of mucosa are left, the entire surface being ulcerated, and presenting a granular appearance. The roentgenogram is characterized by marked narrowing and absence of haustrations in the full extent of the involved colon. The connective tissue found in the inner muscular layer may account for these changes. In four of the five cases, this picture was very definite. In the fourth, it was impossible to make a roentgen-ray examination of the colon, because of the acutely tender condition of the rectum. The stools were usually from five to ten in number, containing a considerable amount of mucopus and blood, frequently in clots. Large hemorrhages occur only occasionally in the adult, but seem to be more frequent in the child. The passing of blood in clots, not intimately mingled with the mucus, is rather characteristic.

Two of the four patients had good appetites, one remarkably good. At no time did this patient have the least indisposition to eat; nor did she have any abdominal symptoms referable to the taking of food. The other three patients had to be constantly coaxed to get them to eat anything at all. Each had considerable tenesmus and cramplike pains in the abdomen, which may have accounted for the lack of appetite. All four patients were markedly emaciated, probably owing to the toxemia and to the rapidity with which the food was passed through the intestinal canal. If there is no complication, the patients are usually free from fever. During the entire stay in the hospital, the patient in Case 3 was free from fever. In Cases 2 and 4, the patients had fever only when there was other cause for temperature, such as arthritis and perirectal abscess. Acute arthritis was seen only once in this group, but it is encountered quite frequently in adults. Perirectal inflammatory conditions are usually of serious prognostic significance.

The diagnosis of the condition is based on mucopurulent diarrhea, associated with the passage of considerable amounts of blood, usually in clots. There is a persistence of the dysentery in spite of all medical treatment, and absence of any of the usual etiologic factors. The age of the patient at onset was from 8 to 10 years, unless it is assumed that the patient in Case 2 had the colitis from the age of 2½ years. There was a period of about seven years when she was fairly well, and it is questionable whether the condition was chronic during this entire period, or whether it had recurred as a result of a second infection. The leukocyte count was normal in two cases, being between 6,000 and 7,000; in one case, it was 20,000, without anything unusual in the differential counts. The characteristic changes, found on proctoscopic examination, are glazing of the mucosa and, in a later stage, a granular appearance due to multiple ulcerations. Roentgenograms are typical, showing the narrow colon with absent haustra.

PROGNOSIS

Under medical treatment, the outlook is bad. Logan gives a mortality of 7.5 per cent. in his cases. The mortality of 27.5 per cent. in cases in which operation was performed is hardly fair, because it includes patients that were doing badly in spite of medical treatment. All of the four patients in the series did poorly under medical treatment alone, and improved only after surgical intervention. In two cases a colostomy, in the third an appendicostomy, and in the fourth an ileostomy (Brown operation) was performed, by means of which the lower bowel could be constantly irrigated with saline solution; and with double opening of the ileostomy, no feces reach the colon. Two of the patients are virtually well, the inflammatory condition in the colon having almost completely subsided; and they are feeling practically normal. The other two patients did not improve, in spite of operation. Unquestionably, the complicating infection around the rectum and in the psoas muscle determined the fatal outcome in one, and the lack of resistance, preventing normal healing, in the other. In cases of this kind, medical treatment, consisting of saline irrigations and large doses of bismuth by mouth, should be tried. Recently, Logan[5] has reported several cases in which the patients improved markedly under massive doses of iodin by mouth. If the patient does not improve in the course of six weeks or two months, under medical treatment, it is advisable to operate. The operation of choice is unquestionably the one devised by Brown, consisting of an ileostomy with the establishment of a complete fecal fistula, through the lower loop of which the colon can be irrigated. It is wise to let considerable time elapse before closing the ileostomy opening. An operative mortality of 50 per cent. is extremely high, but it seems certain that, without operation, there would have been a 100 per cent. mortality. If the experiences in the adult are taken into account with the frequent recurrence after closure, the question of a permanent fistula must be considered.

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5. Logan, A. H.: Three Cases of Chronic Ulcerative Colitis Cured by Iodin, M. Clin. N. America (July) 1923.

REPORT OF A FATAL CASE OF KERATOMALACIA IN AN INFANT, WITH POSTMORTEM EXAMINATION *

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It has been known for some time that xerophthalmia and keratomalacia will develop in animals maintained on a diet deficient in fat soluble A vitamin. Cases of xerophthalmia and keratomalacia in children have also been reported for a number of years, but it is only recently that the occurrence of these conditions has been correlated with the experimental work on animals. We have had the opportunity of observing a case of keratomalacia in an infant which terminated fatally and in which we were able to obtain a complete postmortem examination. In addition to the lesions occurring in the eyes, the microscopic examination showed extensive changes in many other organs of the body. It is for this reason that this case seems of especial interest.

REPORT OF CASE

History.—M. K., a girl, white, aged 5 months, born at full term after a normal delivery, and weighing at birth 6½ pounds (2,954 gm.), gave an entirely negative family history. She was nursed for one month, at the end of which time she was weaned and put on a top milk dilution. This feeding was changed at the end of one month to a formula of condensed milk, a 1 : 10 dilution. Five ounces was given every three hours. She continued to receive this feeding up to the time of admission, a period of three months. At first, she took her feedings well, but for two months prior to admission, she had been refusing large quantities. The total daily intake rarely exceeded 10 ounces. There were no gastro-intestinal upsets at any time, but the baby failed to gain. There was no history of acute illness except frequent colds, characterized by lachrymation and coryza. The last attack had its onset two weeks before admission to the hospital. For one week, the parents had noticed that the eyes appeared dull, as if covered by a film. For two days, she had been drowsy and had refused a large part of her feedings.

Physical Examination.—On admission, the infant was undernourished and underdeveloped, weighing only 6½ pounds. She appeared in a stuporous condition and reacted poorly to external stimuli. The skin showed marked loss of elasticity and in addition had a distinctly waxy feel. There was slight desquamation on the abdomen. The eyes showed marked injection of the conjunctivae, which were dry and wrinkled in appearance, and there was an accompanying photophobia. The corneae were dry and had a dull, ground-glass appearance. The pupils were contracted. The rest of the physical findings were essentially negative.

Laboratory Findings.—The white blood count was from 29,000 to 31,000; the red blood count, 4,600,000; hemoglobin (12 gm. per hundred cubic centimeters), 91 per cent.; blood culture, sterile; blood Wassermann reaction, negative; urine, entirely negative; tuberculin reaction, negative.

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* Received for publication, Aug. 14, 1923.

* From the Infants' Hospital and departments of pathology and pediatrics, Harvard Medical School.

Course.—The baby lived for eighteen days after admission. During this period, she had an irregular temperature between 99 and 104 F. She remained in a semistuporous condition. Although she took a high caloric feeding of whole lactic acid milk fairly well, she failed to gain in weight. The eye condition grew progressively worse, and corneal ulcers developed in both eyes, accompanied by hypopyon. The day before demise, there was a perforation of the left cornea. The dehydration was relieved by the administration of fluids parenterally, but the skin still maintained its peculiar waxy feel. Administration of cod liver oil was instituted on admission. The dose at first was 3 minims three times daily, and this was rapidly increased up to 1 dram three times daily. Death occurred on the nineteenth day.

The important features in the history were briefly as follows: For a long period of time the baby had been fed on condensed milk, a food deficient in fat and protein and necessarily low in fat soluble A vitamin. We have made no attempt to review the literature on this subject, as this has been done in a recent article by Ross.[1] In the four cases reported by him, all the patients had been fed almost exclusively on condensed milk. The deficiency of fat in the diet was also a prominent feature in the large group of cases reported by Mori.[2] His series consisted largely of cases in older children, from 3 to 5 years of age, who had been receiving a diet consisting largely of cereals and vegetables. Bloch [3] has also reported two series of cases of xerophthalmia in infancy, in both of which there was a history of dietary deficiency in fat. The feedings in his cases consisted almost entirely of separator skim milk or buttermilk. In the light of the experimental work which has been done on animals in producing xerophthalmia by a diet lacking the fat soluble A factor, it would seem extremely likely that the human cases are due to a similar deficiency. However, in the latter, it has been impossible to control the other factors, and it is not improbable that some other element, such as the extreme malnutrition, may play a rôle in producing the condition.

The administration of cod liver oil in our case was unsuccessful, although treatment was started soon after the eye changes had been noted. However, this failure to respond to treatment is easier to understand in the light of the extensive pathologic changes found throughout the body. That these changes were of long standing seems certain.

Necropsy Report.—Body: The body was that of a poorly developed and poorly nourished infant, 57 cm. long. The skin was smooth and white, rather dry, and somewhat inelastic. Scalp, ears, nose and mouth were negative.

Eyes: The conjunctiva had a very finely granular surface. The cornea was clouded. Near the center of the cornea of the left eye, there was a rounded excavation, about 4 mm. in diameter, with a slight gray base, and in its center a small hole about 0.5 mm. in diameter, which apparently communicated with the anterior chamber of the eye. The cornea in this excavated area was opaque. The fluid in the anterior chamber was definitely cloudy. Near the center of the right cornea, there was an excavated area about 3 mm. in diameter, with a light gray base. The cornea in this area was opaque.

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[1] Ross, S. G.: Nutritional Keratomalacia in Infants, Am. J. Dis. Child. **22**:232 (Sept.) 1921.

[2] Mori: Ueber den Sogenannten Hikan, Jahrb. f. Kinderh. **59**:175, 1904.

[3] Bloch, C. E.: Klinische Untersuchungen über Dystrophie und Xerophthalmie bei jungen Kindern, Jahrb. f. Kinderh. **89**:405, 1919.

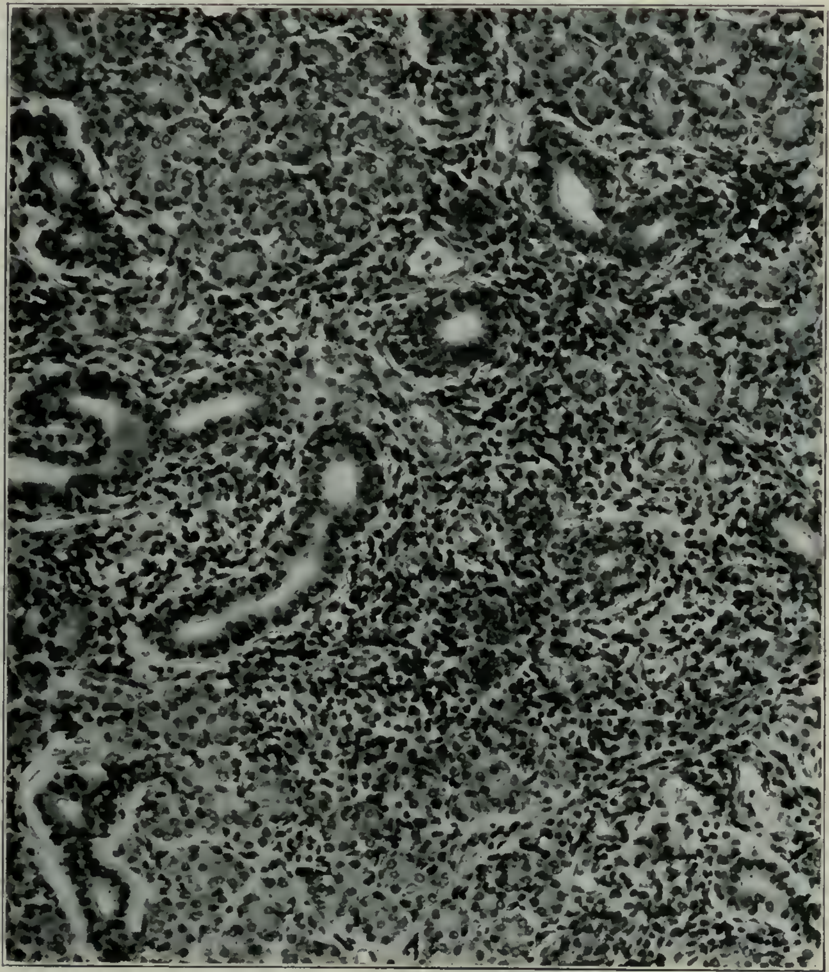

Fig. 1.—Submaxillary gland. In the neighborhood of the ducts, there is an extensive infiltration with leukocytes.

Peritoneal cavity: This was negative.

Pleural cavities: The visceral and parietal pleurae were adherent posteriorly by easily broken fibrinous adhesions. Other portions of the pleural cavities were free. The pleura elsewhere was smooth. There was no free fluid.

Mediastinum: The thymus weighed 1 gm. The mediastinal lymph nodes were negative.

Pericardial cavity: The cavity contained about 5 c.c. of slightly turbid light yellow fluid. The pericardium was smooth and glistening.

Heart: The weight was 17 gm.

Lungs: The right lung weighed 54 gm.; the left, 44 gm. In the upper right lobe posteriorly and in the upper portion of the lower left lobe, there were deep red firm areas. Bullae containing air were found in various places on the surfaces of both lungs, usually in the interlobar septums. On section, a cavity about 1.5 cm. in diameter, with numerous out-pocketings, was found in the center of the consolidated portion of the right upper lobe. This cavity contained a thick mucoid, greenish yellow liquid, which was stringy and did not wash out readily. In other consolidated portions of both lungs, other small collections of liquid of a similar character could be seen. These suggested collections of purulent material in bronchi. The bronchial lymph nodes were red but were not definitely enlarged.

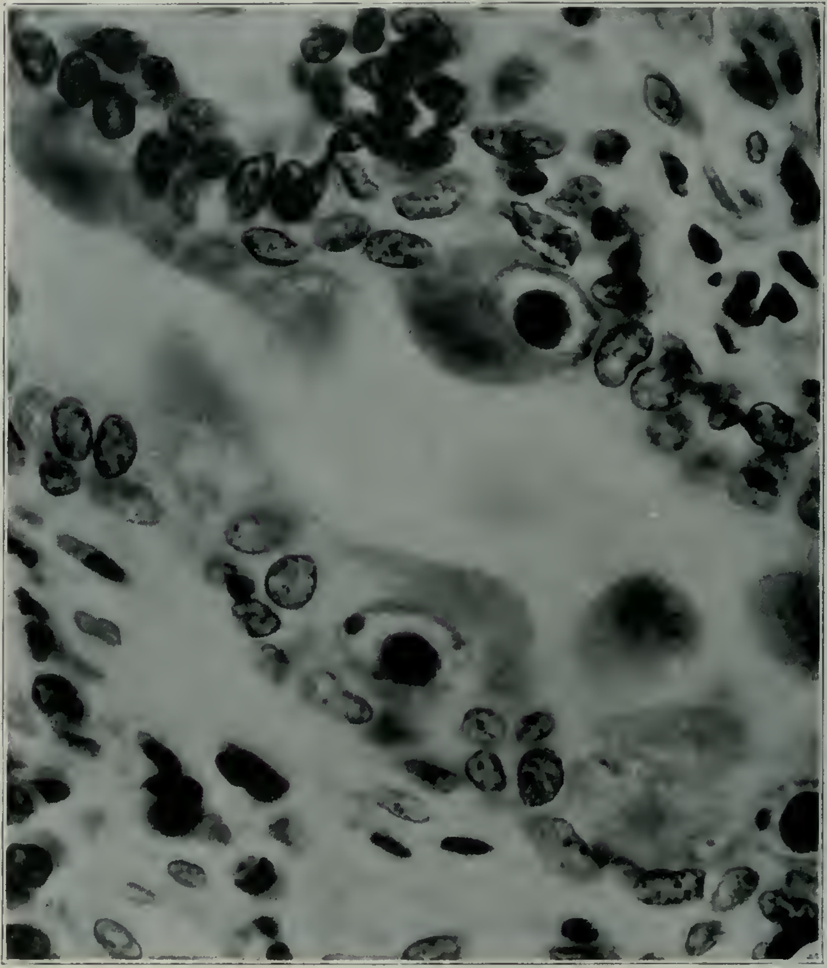

Fig. 2.—Submaxillary gland. A high power photograph of one of the ducts, showing swollen epithelial cells and the peculiar nuclear inclusion bodies.

Spleen: The weight was 12.5 gm.

Liver: The weight was 145 gm.

Gallbladder and gastro-intestinal tract: These were negative.

Pancreas: The weight was 2 gm. The surfaces were smooth. The color was gray. Here and there, a lobule with a yellowish cast was noted.

Kidneys: The weight was 30 gm.

Adrenals and Bladder: These were negative.

Aorta: The intima was smooth, gray and glistening throughout.

Genitalia: The uterus, fallopian tubes and ovaries were normal in appearance.

Organs of neck: The walls of the pharynx and larynx were negative. The trachea and esophagus were also negative. The pharyngeal tonsils were small. The submaxillary, sublingual, and parotid glands were not remarkable on gross examination. The thyroid was small but not remarkable on gross examination. There were two parathyroids, both of which were negative.

Brain: The weight was 420 gm.

Middle ears and lachrymal glands: These were negative.

Bone marrow: The bone marrow in the ribs was red and, grossly, negative. At the costochondral junctions, there was a moderate amount of bulging. On section of this portion, the line between bone and cartilage was slightly irregular.

Microscopic Examination.—Heart: In one section, there was a small area just beneath the intima where the myocardium was infiltrated with a small number of polymorphonuclears. In other places, the sections were not remarkable.

Lungs: A striking finding in the lungs was the epithelial lining of the bronchioles, which in many instances was definitely of a stratified squamous type and showed desquamation of the horny superficial portions (Figs. 7 and 8). In places also, there is a definite piling of epithelium (Fig. 7). Sections from the firm area in the right upper lobe showed spaces filled with necrotic material and leukocytes (mostly polymorphonuclear neutrophils). Some of these areas were completely surrounded with bronchial epithelium; others were partly surrounded, and some showed no epithelial cells at the periphery, the walls being composed of granulation tissue. These were bronchiectatic abscesses. The walls of many bronchi, apparently not dilated, were also infiltrated with leukocytes. In adjacent areas, the alveoli were filled with exudate, usually purulent, but in certain areas fibrinous.

Spleen: Some of the splenic nodules contained pale centers, in which there were large mononuclears with abundant cytoplasm. The pulp contained a large number of polymorphonuclear neutrophils.

Liver, gallbladder and bile ducts: These were negative.

Gastro-intestinal tract: Sections from the stomach, pylorus, duodenum, ileum and colon were apparently negative. The lymph nodules of the Peyer's patches contained pale centers which presented a picture similar to that observed in corresponding areas in the spleen.

Pancreas: Changes here were marked, the most striking among these being numerous epithelial lined cystlike cavities (Figs. 4 and 5). There were a few acini which approached the normal in appearance, but for the most part their lumina varied in size from the normal-appearing up to the relatively large cystlike cavities, which were apparently dilated acini. The smaller cystlike cavities were lined with a cuboidal epithelium, but as the cysts increased in size, the tendency toward flattening became more apparent. In the lumina, there were rounded eosin-staining masses, and in some instances numerous polymorphonuclear neutrophils. The islands of Langerhans varied considerably in size and possibly were decreased in number. In places, they were being invaded with polymorphonuclear neutrophils. A section from the head of the pancreas showed a small space lined with stratified cornified epithelial cells filled with keratinized epithelium (Fig. 6). In another small duct, there was a definite piling up of epithelial cells. The supporting connective tissue was increased in amount (Fig. 4). In some areas, there was a marked polymorphonuclear infiltration of both stroma and parenchyma, and in others lymphoid and plasma cells predominated.

Mesenteric lymph nodes: Some of the lymph follicles presented a picture similar to that observed in lymph follicles of the spleen and Peyer's patches.

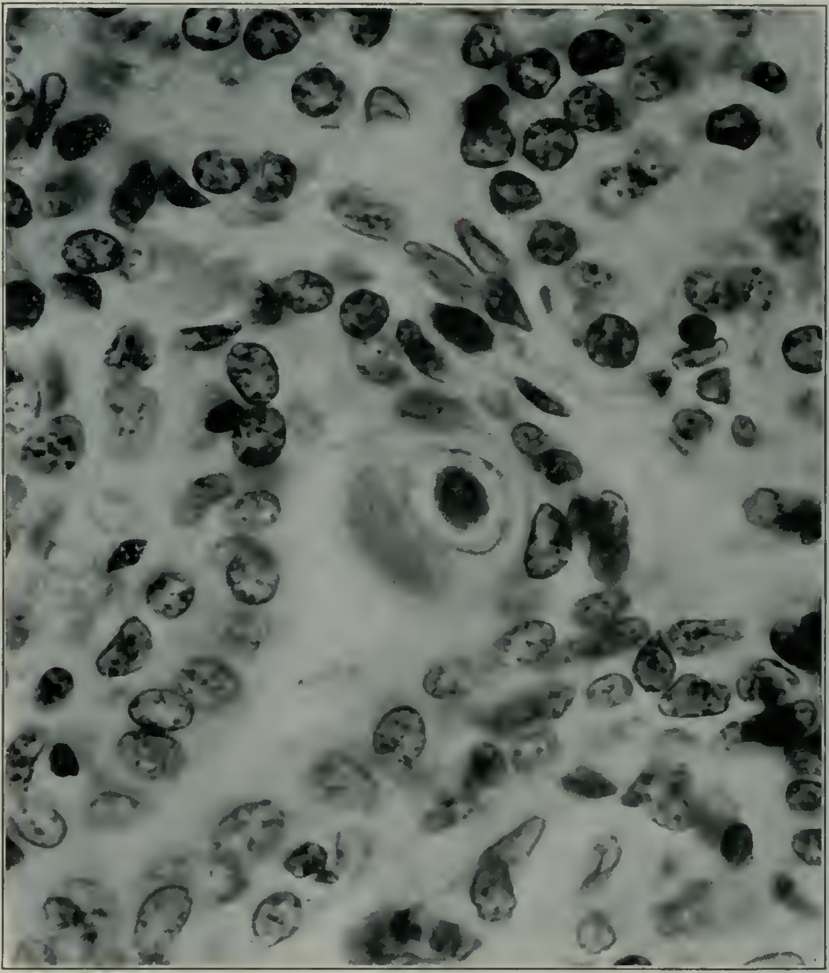

Fig. 3.—Parotid gland. A high power photograph of one of the ducts, showing a swollen epithelial cell containing a nuclear inclusion body.

Kidneys: The glomeruli were not remarkable. In places, the tubular epithelium was perhaps swollen. There were small areas in the connective tissue supporting the epithelial lining of the pelvis which were infiltrated with leukocytes, both polymorphonuclear neutrophils and mononucleated forms.

Suprarenals: These were negative.

Bladder: In the tissue immediately beneath the epithelium, there were areas which showed a slight leukocytic infiltration.

Uterus: Sections from the fundus showed that the lining was nearly replaced by stratified squamous epithelium (Fig. 9). Where so replaced, the uterine glands were absent. This was in marked contrast to the cervical portion, where the lining consisted of a single layer of columnar epithelial cells. The stroma was not remarkable.

Fallopian tubes and ovaries: These were negative.

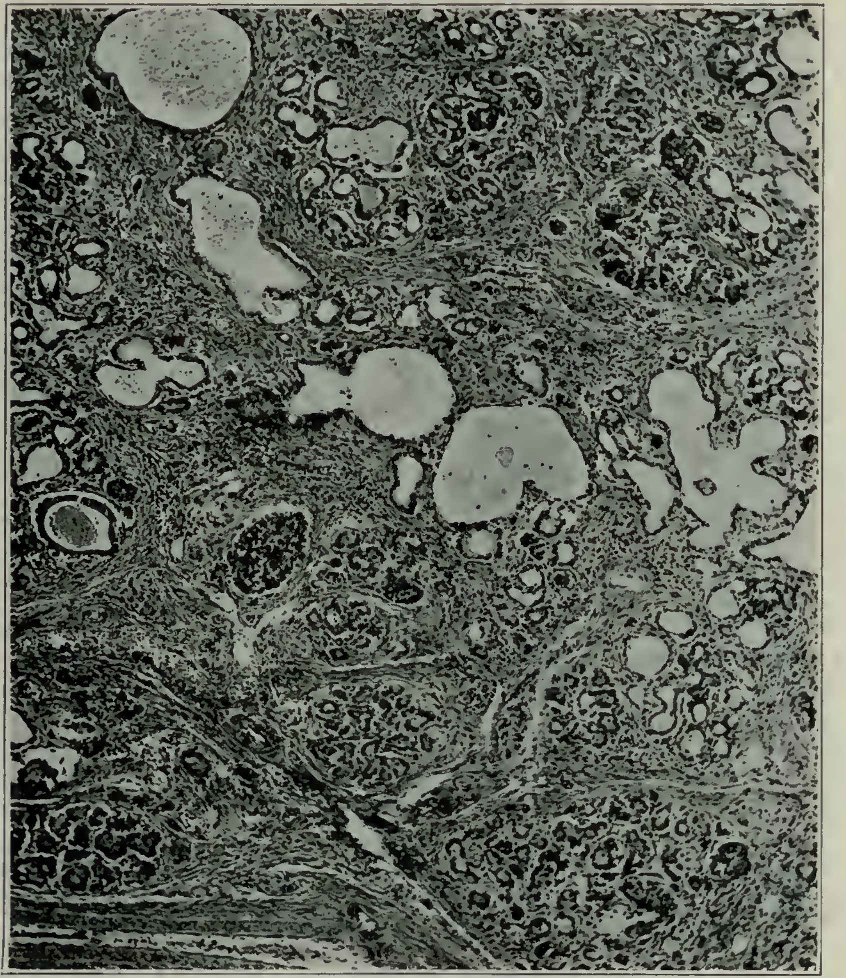

Fig. 4.—Pancreas. A general view, showing epithelial lined cystlike cavities, fibrosis and a leukocytic reaction.

Brain: Sections from the cerebrum and the cord were not remarkable. Sections from the pituitary body were negative.

Thymus: The lobules of the thymus were irregular and were supported by wide bands of connective tissue which contained a few fat cells. In certain areas, the thymic tissue was apparently being replaced by connective tissue.

Thyroid and parathyroid: These were negative.

Tongue: There was a marked desquamation of the superficial layers of keratinized epithelium. The epithelial covering and its supporting tissues were infiltrated with a relatively large number of leukocytes, most of which were polymorphonuclear neutrophils. Occasionally, small groups of muscle fibers and sometimes single fibers were found which stained deeply with eosin and had a waxy, homogeneous appearance, suggesting Zenker's degeneration.

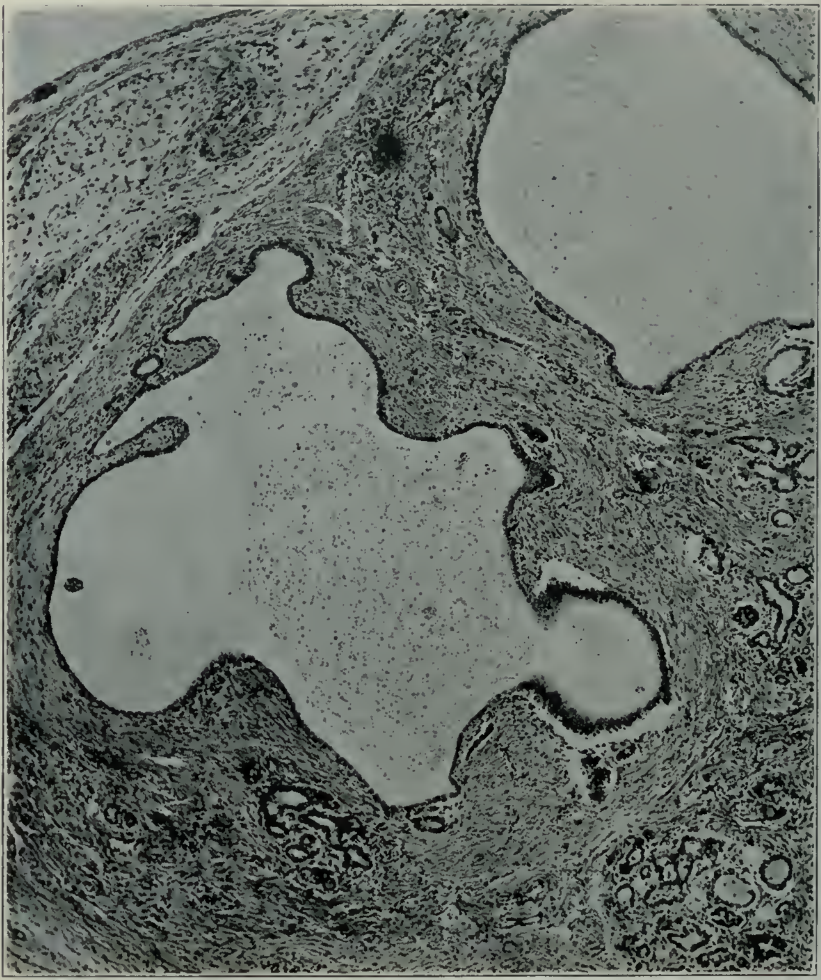

Fig. 5.—Pancreas. Epithelial lined cystlike cavities and fibrosis.

Pharyngeal mucous membrane: There was a moderate inflammatory reaction involving the epithelial covering and its supporting connective tissue, which resembled but was less marked than that observed in the tongue.

Larynx: There was a moderate degree of desquamation of the superficial portions of the lining epithelium. There was also an inflammatory reaction resembling that observed in the pharyngeal mucosa. The secreting cells of some of the mucous glands were in places flattened out along the periphery and contained very little cytoplasm. Their nuclei were small, deeply staining, elongated masses, closely applied to the basement membrane.

Trachea and primary bronchi: In the trachea, just below the vocal cords, there was a slight degree of cornification of the superficial layers of epithelium. Sections from lower levels of the trachea and from the primary bronchi did not show this change. There was a slight acute inflammatory reaction similar to that observed higher up in the trachea and in the primary bronchi. In a few instances, the mucous glands surrounding the primary bronchi presented a picture similar to that described in the larynx.

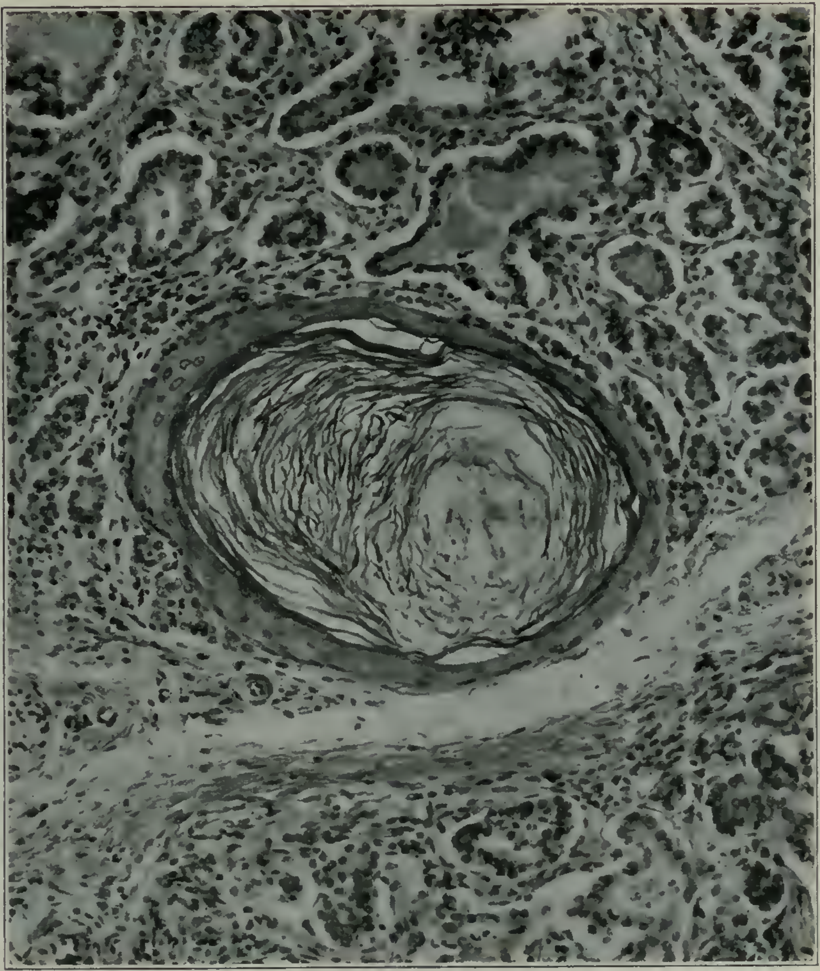

Fig. 6.—Pancreas. One of the pancreatic ducts, showing keratinization and desquamation of epithelium with complete occlusion.

Esophagus: There was some slight cornification of the superficial portions of the mucous membrane, perhaps not more than normal. In sections taken from several levels, there was an acute inflammatory reaction of moderate intensity, but less marked than that observed on the tongue. Certain of the mucous glands were lined with very much flattened cells with deeply staining basophilic nuclei, which were stretched out along the basement membrane. A few of the glands were lined with epithelial cells which approached the normal. Certain of the ducts were lined with stratified squamous epithelium.

Lachrymal gland: The tissue around the ducts was infiltrated with a small number of mononuclear leukocytes, most of which were lymphoid and plasma cells. The epithelial cells lining the acini were not remarkable. It is possible that the lumina of most of them were slightly larger than those of normal glands, but this point could not be stressed. Some of the lumina contained a small amount of finely granular eosin-staining material. The epithelium lining the ducts was not remarkable.

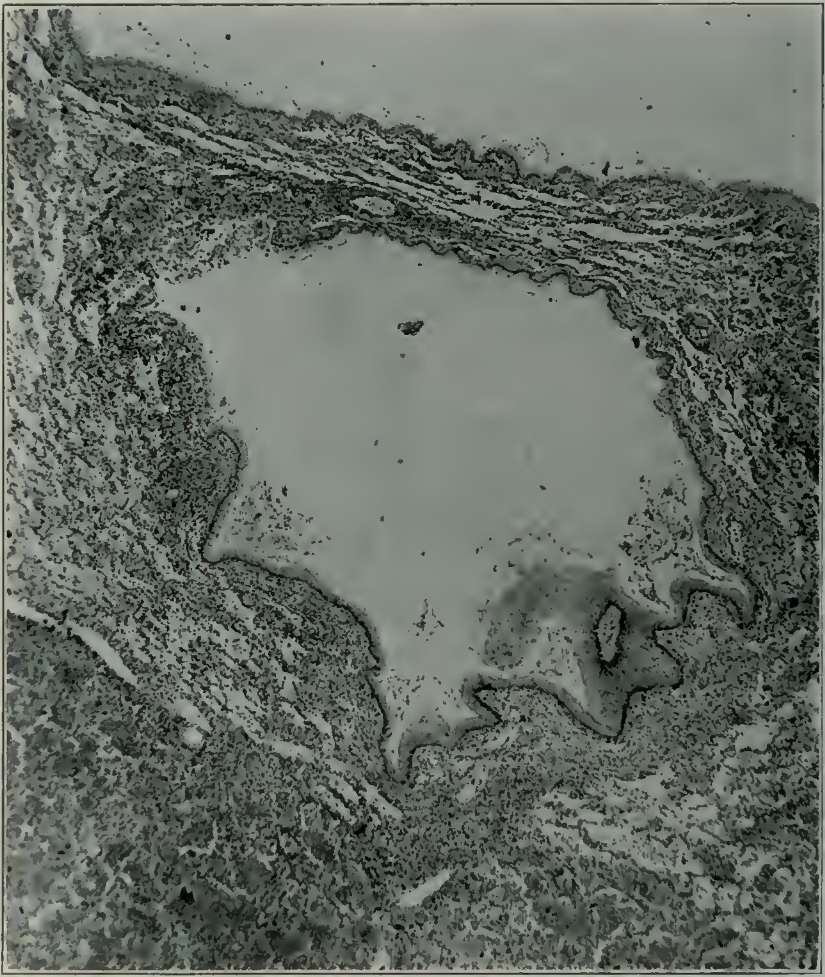

Fig. 7.—Lung. A bronchus, showing stratified squamous epithelium.

Submaxillary gland: In the neighborhood of the ducts, there was rather extensive infiltration with leukocytes. Lymphoid and plasma cells predominated, but in addition there were large mononucleated cells with large vesicular nuclei and rather abundant foamy cytoplasm. In the epithelial lining of the ducts, however, there was a peculiar change. Among the epithelial cells lining the ducts, very large cells were frequently encountered. The cytoplasm of these cells encroached on the lumen and the adjacent epithelial cells. The cytoplasm was characterized by round clusters of minute basophilic granules. The nuclei of these cells, which were situated near the base, were frequently twice the size of the average nucleus in the neighboring epithelial cells. The nucleus was sharply demarcated by a bluish (hematoxylin stain) outline (nuclear membrane), which frequently enclosed a deeply stained (bluish) structureless body resembling a nucleolus. Separated from the periphery by a clear zone was a large mass rounded or irregular in shape, often finely vacuolated (Figs. 2 and

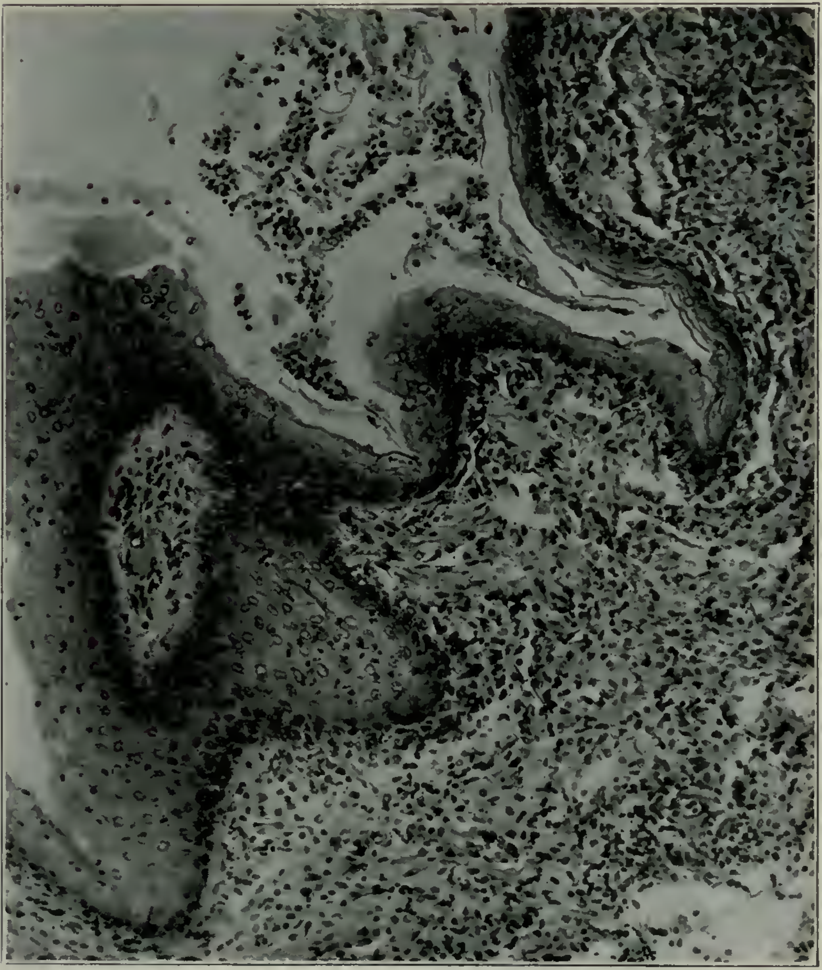

Fig. 8.—Lung. A higher power photograph of the bronchus shown in Figure 7, presenting in greater detail the character of the stratified squamous epithelial lining.

3). In some cases, the central blue mass was surrounded by a reddish zone; in others the entire mass stained with the acid stain, while in a few instances it was entirely absent. In the latter case, the peripheral ring contained eosin-staining granules. One section showed a duct lined with flattened epithelial cells with amorphous eosin and hematoxylin-staining masses. In the neighborhood of ducts in which there was an extensive leukocytic infiltration, some of the acini were undergoing destruction. The more remote acini were for the most part unchanged, though some of the cells contained a pale swollen cytoplasm showing a fine reticulum. The nuclei were pushed toward the basement membrane, and in some cases were entirely missing. The lumen was usually obliterated by the swollen cells.

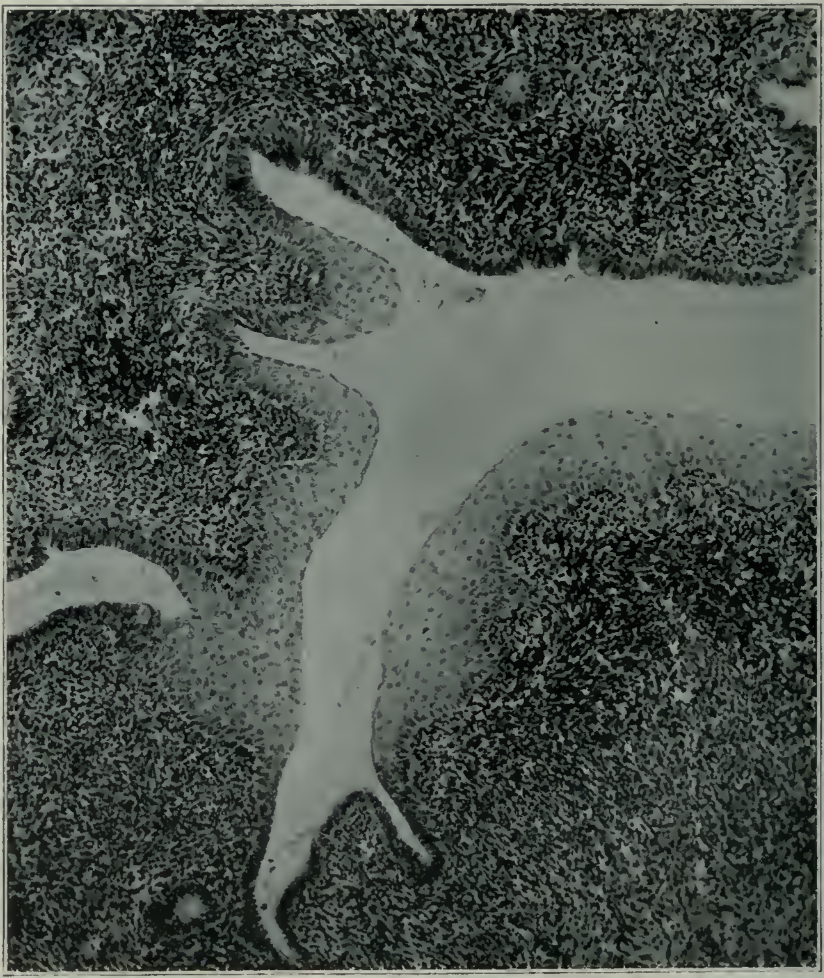

Fig. 9.—Uterus. The fundus of the uterus is lined in places with stratified squamous epithelium.

Parotid gland: The reaction in the parotid gland resembled very much the reaction found in the submaxillary gland. There were, however, no ducts lined with flattened epithelial cells. The inflammatory reaction in places was more pronounced. In a number of places, the glandular tissue was apparently replaced by fat; which suggested atrophy.

Sublingual gland: The glandular tissue for the most part was not remarkable. Around the ducts, only an occasional lymphoid and plasma cell could be seen. In one portion of one of the glands, however, there was an area infiltrated with leukocytes, chiefly of the mononuclear type. The epithelial cells lining the acini in this area were shrunken, and the lumina were filled with eosin-staining material, while occasionally epithelial cells were found which were being invaded with polymorphonuclear neutrophils.

Yudkin and Lambert,[4] in a recent study of keratomalacia in rats, found slight changes in the lachrymal glands of animals showing early eye lesions; wide spread suppurative inflammatory processes in animals with advanced eye lesions, and mononuclear cell accumulations and foci of atrophy or fibrosis in animals that were cured. In the severely affected lachrymal glands, Mori [5] found that the acinar cells were shrunken, and that these cells no longer showed secretory zones.

In the meibomian glands, Mori [5] often found cystic dilatation of the ducts. The lumina of the acini of the harderian glands were dilated and empty, or narrowed by the swelling of the secretory cells. The secretory cells of the salivary glands were much shrunken. The epithelium of the intralobular ducts was also much shrunken and irregular. In the principal ducts, there was a remarkable degree of cornification and desquamation of epithelium. Other secretory organs, such as liver, bowel, kidneys, thyroid and pancreas, showed no remarkable change, except in the case of the pancreas, where, in one instance, the cells showed extensive vacuolation. The mucous membrane of the mouth was dry clinically and at necropsy. The mucosa of the larynx and trachea showed marked "xerotic" (keratinizing) changes.

Eye changes as observed by Wason [6] are briefly as follows: hyalinization or necrosis of the outer layer of corneal epithelium; exudation of serum and cells into the epithelium and stroma; proliferation of blood vessels, and fibrosis. In the advanced cases, invasion of the anterior chamber and sometimes of the posterior chamber may result.

COMMENT

In the following paragraphs, we wish to compare our findings with those in experimental animals. The lesions observed by us in the

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4. Yudkin, A. M., and Lambert, R. A.: Lesions in the Lachrymal Glands of Rats in Experimental Xerophthalmia, Proc. Soc. f. Exper. Biol. & Med. **19**:376, 1922.

5. Mori, S.: Changes in the Para-Ocular Glands which Follow the Administration of Diets Low in Fat-Soluble A; with Notes on the Effect of the Same Diets on the Salivary Glands and the Mucosa of the Larynx and Trachea, Bull. Johns Hopkins Hosp. **33**:357 (Oct.) 1922.

6. Wason, Isabel M.: Ophthalmia Associated with a Dietary Deficiency in Fat Soluble Vitamin A, J. A. M. A. **76**:908 (April 2) 1921.

lachrymal glands were not marked and consisted chiefly of a small round-cell infiltration of the tissues about the ducts. The reaction resembled the reaction described by Yudkin and Lambert[4] in the lachrymal glands from cured cases observed in connection with their experimental work on rats. One naturally wonders, therefore, whether the addition of cod liver oil to the diet of the patient may not have had some effect on the lachrymal glands, in spite of the fact that the child grew progressively worse.

In the submaxillary and parotid glands, there were extensive lesions, the most striking of these being the inflammatory reaction about the ducts. In several places, there were also evidences of retrograde changes. The latter were described by Mori.[5] In only one instance did we find a suggestion of cornification of the duct epithelium, which Mori[5] found in many cases.

The sublinguals in general showed little change; but, in one small area, there was a very definite inflammatory reaction. Mori believes that, coincidently with "xerotic" (keratinizing) changes in the ducts and in the parenchymal cells, the ducts are invaded by bacteria producing small abscesses in the gland.

Nuclear inclusion bodies in the epithelium lining the ducts of the parotid and submaxillary glands were not mentioned by Mori. These bodies are reminiscent of those described by Councilman, Magrath and Brinckerhoff[7] in cases of vaccinia and variola. They resemble even more closely the "herpes bodies" described by Lipschultz[8] in the lesions of herpes simplex and more recently mentioned by Fuchs and Landa,[9] Friedenwald[10] and Goodpasture and Teague.[11]

The eye changes in our cases were apparently similar to those observed in the disease when experimentally produced. Stephenson and Clark,[12] working with rats, were unable, prior to bacterial invasion of the eye, to demonstrate any histologic changes directly attributable to dietary deficiency. In other words, the cornea appeared normal until the onset of purulent inflammation. Mori feels that the lesions in the lachrymal glands are the most important in the pathologic picture, and that the changes in the glands would seem to cause the lesions in the cornea and conjunctiva. He states that he observed many vacuoles in the cells of the pancreas in one case. Wason does not describe changes in the pancreas. In our case, however, there were extensive lesions. Certain of the ducts showed definite keratinization of epithelium and in one instance complete occlusion (Fig. 6). There were many cystlike epithelial lined cavities, a definite inflammatory process and fibrosis.

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[7] Councilman, W. T.; Magrath, G. B., and Brinckerhoff, W. R.: Etiology of Variola, J. M. Res. **9**:372 (May) 1903.

[8] Lipschutz: Ueber Nachweis und Bedeutung der 'zoster' und 'Herpeskoerperchen' ('alpha' und 'beta'—'Herpeskoerperchen') in der geimpften Kaninchenhornhaut, Verhandl. d. ausseroid. Tag. d. oph. Gesellsch. Berl. (1921), 1922, pp. 369-372.

[9] Fuchs and Landa: Zur Aetiologie der Keratitis dendritica, Ztschr. f. Augenheilk. **49**:9, 1922.

[10] Friedenwald, J. S.: Studies in the Virus of Herpes Simplex, Arch. Ophth. **52**:105 (March) 1923.

[11] Goodpasture, E. W., and Teague, O.: The Occurrence of Intranuclear Inclusion Bodies in Certain Tissues of the Rabbit Inoculated Directly with the Virus of Herpes Labialis, Proc. Soc. Exper. Biol. and Med. **20**:400, 1923.

[12] Stephenson and Clark: Keratomalacia Among Rats, Biochem. J. **14**:502 1920.

In the lungs, there was extensive keratinization of bronchial epithelium in many places. In addition, there were bronchiectatic cavities, bronchiectatic abscesses, extensive peribronchitis and interstitial emphysema. Although the evidence at hand does not permit us to come to any positive conclusion regarding the relationship of the keratinization of bronchial epithelium to the bronchiectases, it seems probable that occlusion of bronchioles by desquamated keratinized epithelium was an important factor. Mori[5] found marked keratinization of the mucous membrane of the larynx and trachea, but did not mention the involvement of bronchi.

The changes in the character of the epithelium in various parts of the body were interesting. The tendency for epithelium of one type to change over into another type was present in various places. Such a tendency was found in the case of the epithelium lining the fundus of the uterus (Fig. 9), the epithelial lining of the trachea, the epithelium lining bronchi (Fig. 8), the epithelium lining certain of the pancreatic ducts (Fig. 6) and, to a less marked degree, the epithelium lining of one of the submaxillary ducts. In these places, we found stratified squamous epithelium, with cornification of the superficial portions. In Mori's work, he mentions keratinization in many places; namely, the conjunctivae, ducts of salivary glands, ducts of meibomian glands, larynx and trachea.

SUMMARY

Our patient, an infant, 5 months old, had been fed exclusively on condensed milk for a long period of time. When the baby first came under observation, it was markedly underdeveloped and emaciated; its skin was dry and had a peculiar waxy feel, and the conjunctivae were dull and the corneas cloudy. In spite of the administration of cod liver oil, the baby's condition grew progressively worse. Corneal ulcers developed, followed by a perforation of the cornea in one eye. Death occurred on the nineteenth day.

At necropsy, the eye lesions were the most striking of the few that were observed on gross examination. Microscopic study, however, revealed changes in many organs. In the lachrymal and salivary glands, there were inflammatory lesions; and in the epithelium lining the submaxillary and parotid gland ducts, peculiar cell changes and nuclear inclusion bodies were found. The pancreas showed keratinization of the epithelium in certain ducts, many large and small epithelial lined cystlike cavities, a marked inflammatory process and extensive fibrosis. The lungs showed keratinization of the bronchial epithelium, a marked peribronchitis, bronchiectatic cavities, bronchiectatic abscesses and interstitial emphysema.

Of peculiar interest is the change of a columnar epithelium to a stratified keratinized type found in the uterine mucosa, bronchi and pancreatic ducts, and, to a less marked degree, in one of the ducts of the submaxillary gland and the trachea.

To the mechanical effect of desquamated keratinized epithelium, we are inclined to attribute the pancreatic cysts and bronchiectases.

A CASE OF POSTSCARLATINAL PHLEBITIS *

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Phlebitis or thrombophlebitis is apparently a rare complication following scarlet fever. In 1882, Southey [1] reported a case of symmetrical gangrene of the skin of the abdomen in a child, 5 years old. It occurred fourteen days after the onset of the scarlatinal eruption. Sloughing took place on the eighth day, and healing was not complete until eight weeks later. Davies, in 1891, showed a girl of 9, who had developed symmetrical gangrenous areas over the legs, which spread rapidly to other parts of the body. This occurred during the third week of the scarlet fever and the patient died two days after the appearance of the first area of necrosis.

Wilson,[2] in 1895, published a case of symmetrical gangrene of the face and sacral region following scarlet fever. The boy was 6 years old, and the gangrene started on the tenth day of convalescence. The patient died. In 1897, Pearson and Littlewood [3] reported a case of dry gangrene of both lower extremities complicating ordinary scarlet fever in a boy of 4. Recovery followed amputation of the limbs. Subsequent examination revealed a thrombosis of the popliteal artery and vein of both legs. They cite a case published by Holmes [4] of gangrene of the left leg complicating scarlet fever in a woman, aged 40.

Eichkorst,[5] in 1901, demonstrated a case of gangrene of the left leg and foot in a girl of 4, occurring in the third week of convalescence. Recovery followed amputation. There was a thrombosis of the left popliteal artery as a result of an endarteritis. He mentioned a case published in the *Jahrbuch fur Kinderheilkunde,* 1860, which we have been unable to obtain. A boy, 9 years old, developed gangrene of left leg and foot, later involving the right side also. The boy died and at necropsy a thrombosis of the iliac artery and vein was found.

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* Received for publication, Aug. 11, 1923.

* From the Minneapolis General Hospital.

1. Southey: Case of Symmetrical Gangrene of the Skin of the Abdomen in a Child, Brit. M. J. **2**:1904 (Dec. 2) 1882.

2. Wilson, J. C.: A Case of Symmetrical Gangrene of the Face and Sacral Region Following Scarlet Fever, Tr. Am. Pediat. Soc. **7**:109-118, 1895.

3. Pearson, A. E., and Littlewood, H.: A Case of Dry Gangrene of Both Lower Extremities Complicating Ordinary Scarlet Fever, Lancet **2**:84-85 (July 10) 1897.

4. Holmes' System of Surgery, quoted by Pearson and Littlewood (Footnote 3).

5. Eichkorst, Hermann: Ueber Brand an Armen und Beinen nach Scharlach und anderen Infectiouskrankheiten, Deutsch. Arch. f. klin. Med. **70**:519-558, 1901.

In 1902, Moizard and Ullman[6] reported a case of phlebitis scarlatinosa. This is the only case resembling our own in any respect that we have been able to find. Four days after the onset of the scarlet fever, the patient, a girl of 4½ years, began to complain of pain and swelling of the right arm and forearm. A diagnosis of phlebitis of the axillary and brachial veins was made. *Streptococcus pyogenes* was obtained from blood culture. The patient recovered.

They were able to collect four other cases of phlebitis from the literature. Two were cases of phlebitis of the sinus dura matris; one, a phlebitis of the facial veins; and the fourth a case of sinus thrombosis. All ended fatally.

Netz,[7] in 1904, published a case of symmetrical gangrenous spots following scarlet fever in a girl 7½ years old. They were located in the region of the nervous cutaneous brachialis medialis and the intercostobrachial. They were also present on the buttocks and the right thigh, and later, on the foot. Recovery was said to follow local applications of peroxid.

In 1912, Escherich and Schick,[8] in an extensive monograph on scarlet fever, mention the rarity of this condition. Schick cites one case that came under his care. A 9-year-old boy, showing a postscarlatinal nephritis, developed a swelling and bluish discoloration of the left calf accompanied by a paresthesia. Eight days after the onset, both extremities became cold and lifeless. Needle pricks were not felt. Sixteen days after the onset, the pulsation of the left crural artery could not be felt. Gangrene developed, extending up to the middle third of the left thigh. The right lower extremity also showed severe circulatory disturbances. The patient died, and at the postmortem a thrombosis of the iliac artery and vein was found.

Dublin, in a study of 1,153 cases of scarlet fever, with especial reference to their sequelae, found no record of a case of phlebitis. Riesman, in a thorough discussion of phlebitis following various infections and infectious diseases, fails to include scarlet fever. Nobecourt and Tournier,[9] in 1915, reported two cases of phlebitis of the extremities following scarlet fever. Both patients were young men, 29 years old. The phlebitis appeared late in both cases, on the thirty-seventh day in Case 1 and on the forty-fifth day in Case 2. In Case 1, the phlebitis was unilateral and was preceded, accompanied and followed by rheumatism of the joints, endocarditis and pericarditis. In Case 2 the phlebitis involved both lower extremities. The course in both cases presented the classic symptoms of phlegmasia alba dolens. Both patients recovered.

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[6] Moizard, M., and Ullman, M.: Phlebitis scarlatinosa, Arch. de med. d. enf. **2**:601 (Oct.) 1899; abstr., Arch. f. Kinderh. **34**:315, 1902.

[7] Netz: Gangran bei Scharlach, Therap. Monatsh. **18**:353-354 (July) 1904.

[8] Escherich, Theodore, and Schick, Bela: Scharlach, Vienna, Alfred Hölder, 1912, pp. 89-90.

[9] Nobécourt and Tournier: Phlebitis Following Scarlet Fever, Bull. et mém. Soc. méd. d. hôp. de Paris **39**:807, 1915.

REPORT OF CASE

History.—A boy, aged 6, admitted to the Minneapolis General Hospital, complaining of pain and swelling in the left lower extremity, had had scarlet fever, with onset, Jan. 15, 1923, and had been released from quarantine two weeks before the present admission (Feb. 24, 1923). Three days after, when getting out of bed, he began to complain of pain in the left thigh. The pain gradually became more severe and the thigh showed marked increase in size.

Examination.—The patient was well developed and somewhat undernourished, very toxic, and in a semicomatose state. Except for the condition of the left lower extremity, the physical findings were entirely negative. The thigh especially was markedly swollen and presented the appearance of a tumor mass on its inner surface. There was a large gangrenous, necrotic area over the heel. The entire extremity was very painful to the touch. Pulsation of the dorsalis pedis could be detected.

Laboratory data on entrance showed no urinary findings of importance. The blood examination throughout the course of the illness revealed: approximately 80 per cent. hemoglobin; 4,700,000 red blood cells; 18,000 leukocytes, with 56 per cent. polymorphonuclears and 44 per cent. lymphocytes. The Wassermann reaction was negative. Repeated blood cultures were negative.

Subsequent Course.—February 26: The temperature was 101 F.; the pulse, 100. There was no change in the general condition, except for more localized involvement along the course of the saphenous vein. The right lower extremity showed some tenderness and swelling. The roentgen-ray examination of the long bones revealed no evidence of a pathologic condition.

March 4: The temperature was 100 F.; the pulse, 140. The condition had grown worse. The involvement of the right side was as extensive as that of the left. Clonic contractions of the muscles of the entire right lower extremity, lasting from five to ten minutes, occurred several times.

March 5: The patient was extremely toxic. Clonic contractures of the right upper extremity appeared, for no apparent reason. The leukocyte count was 17,500.

March 8: Contractures ceased two days previous. The mass on the inner surface of the right thigh was slowly disappearing. A purplish, gangrenous area, 4 by 6 cm., appeared in the morning on the median side of the middle third of the right leg. The patient was developing a marked collateral circulation of the superficial vessels of the thighs, abdomen and thorax. The venous structure on the abdominal wall resembled a caput medusae.

March 9: Tenderness, rigidity and muscle spasm of the entire right abdominal wall were noted.

March 11: The general condition was slightly better. The condition of both lower extremities was unchanged. There had been no extension of the necrotic areas.

March 15: Improvement had been marked for the past three days, but the local condition showed no change.

March 20: The patient was steadily growing stronger. The superficial veins showed considerable thickening of the walls and could easily be traced on palpation. An extensive collateral circulation had developed.

March 26: Local swelling of the thighs was disappearing and pain on pressure was not so severe.

April 8: The temperature was 102 F. the past two days. Examination shows Koplik spots in the cheeks. The patient was transferred to the contagious service.

April 17: On his return, edema of the extremities was practically gone. The general condition was very good. The necrotic areas showed evidence of healing.

April 23: The patient had been gradually allowed to sit up and take a few steps.

The patient was discharged to the outpatient service.

He has been seen repeatedly at regular intervals since his discharge, and there has been no return of the infection.

COMMENT

The apparent rarity of this condition, the extensive involvement of both lower extremities with the presence of necrotic, gangrenous areas, the formation of a vast compensatory collateral circulation, and, finally, the recovery of the patient following a purely symptomatic treatment make this a case of unusual interest.

ALLERGY TO COW'S MILK IN INFANTS WITH NUTRITIONAL DISORDERS *

A PRELIMINARY REPORT

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AND
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On the basis of clinical evidence, feeding experiments and the results of investigations on animals, one of us (O. M. S.) has, for some years, considered the possibility that the biologic character of the protein of cow's milk may be a factor in the causation of nutritional disturbances in young infants. The object of this paper is to report data which have a bearing on the subject.

The conception that nutritional disturbances of infants may be due to the absorption of unaltered or slightly altered protein has been discussed by Schlossman,[1] Moro,[2] Finkelstein,[3] Salga,[4] Wernstedt,[5] Lust,[6] Reiss[7] and others, largely on the basis of indirect evidence and without any accompanying data of significance. It is beyond the scope of this paper to discuss the literature, but that will be undertaken in a later and more complete report.

In order for foreign protein to cause a specific reaction in the organism, it must be absorbed in a form unaltered or only partly altered by digestion. Protein which has been digested as far as to the peptones does not cause specific immune reactions, and, according to the current

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* From the Department of Pediatrics, Harvard Medical School, and the Infants' Hospital.

* A preliminary report of part of the investigations on which this paper is based was published in the Proceedings of the Society for Experimental Biology and Medicine **20**:5, 1922.

[1] Schlossman: Ueber die Giftwerkung der Artfremden Eiweiss in der Milch auf der organismus des Säuglings, Arch. f. Kinderh. **41**:99, 1905.

[2] Moro: Kuhmilchpräzipitin im Blute Eines 4½ monate alten Atrophikers, München. med. Wchnschr. **53**:214, 1906.

[3] Finkelstein: Kuhmilch als Ursache Akuter Ernährungs-störungen bei Säuglingen, Monatschr. f. Kinder. **4**:65, 1905.

[4] Salga: Einige Bermerkungen zu den Thema "Arteigenes und Artfremdes Eiweiss" im bezug auf die Säuglings ernährung, Monatsch. f. Kinderh. **5**:213, 1906.

[5] Wernstedt: Zur Frage der Kuhmilchidiosynkrasie im Säuglinsalter, Monatsch. f. Kinderh. **9**:345, 1910-1911.

[6] Lust: Kuhmilch Idiosynkrasie und Anaphylaxie, Med. Klin. **8**:1735, 1912.

[7] Reiss: Zur Lehre von der Intoleranz mancher Säuglinge gegen Kuhmilch, Monatsch. f. Kinderh. **5**:85, 1906.

view, ingested protein is completely hydrolyzed in the intestinal tract to its constituent amino-acids. There is much evidence, however, to indicate that the intestinal tract of infants may be permeable to undigested or partly digested protein. This subject has been considered in detail in a previous communication.[8] It has been shown by Lust,[9] Hyashi,[10] Schloss and Worthen[8] and others that, under certain conditions, the intestinal tract of infants may be permeable to egg protein. Bauer,[11] Modigliani and Benini,[12] Schloss and Worthen[8] and others have demonstrated the same to be true of milk protein. In the investigations cited, the foreign protein was demonstrated in the blood or urine by means of precipitin tests or by anaphylactic tests on guinea-pigs. The permeability of the intestines to foreign protein has been demonstrated with greatest frequency in marasmic infants, or in those suffering from diarrhea.

If undigested or partly digested protein gained entrance to the blood stream through the intestinal wall, the result would probably be the same as if the protein were given parenterally. Under such circumstances, one might expect to find specific antibodies to the protein in the blood. This condition would be analogous to the findings in animals when given intravenous injections of foreign protein and to the demonstration of specific antibodies in the blood of patients after the injection of horse serum, by Moro and Hamburger,[13] Longcope and Rackemann,[14] Weil and others. The matter is probably of more than academic interest; for if the absorption of foreign protein is responsible for symptoms, it would seem most likely that a formation of antibodies has been provoked. Most of the recorded observations on the point have been negative. Moro and Hamburger failed to find either cow's milk protein or a precipitin for cow's milk protein in the blood of infants with gastro-enteric disorders, but Moro [2] found precipitins to cow's milk in the blood of a marasmic infant examined postmortem, and in a marasmic infant, Bauer [11] demonstrated the presence of precipitin to cow's milk, and also obtained a positive complement fixation reaction with milk protein as antigen.

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[8] Schloss, O. M., and Worthen, T. W.: The Permeability of the Gastro-Enteric Tract of Infants to Undigested Protein, Am. J. Dis. Child. **11**:342 (May) 1916.

[9] Lust: Die Durchlässigkeit des Magendarmkanales für heterologes Eiweiss bei ernahrungsgestorten Säuglengen, Jahrb. f. Kinderh. **77**:244, 283, 1913.

[10] Havashi: Ueber die Durchlassigkeit des Säuglingsdarmes für artfremdes Eiweiss und Doppelzucker Monatschr. f. Kinderh. **12**:749, 1914.

[11] Bauer: Ueber den Nachweis der pracipitablen Substanz der Kuhmilch im Blute atrophescher Säuglinge, Berlin klin. Wchnschr. **43**:711, 1906. Ueber die Durchgängigkeit des Magendarmkanals für Eiweissund Immunköper und deren Bedeutung für die Physiologie und Pathologie des Säuglings, Arch. f. Kinderh. **42**:399, 1905.

[12] Modigliani and Benini: Policlinico, December, 1915; abstr. J. A. M. A. **64**:476 (Jan. 30) 1915.

[13] Moro and Hamburger: Wien klin. Wchnschr. **16**:445, 1903.

[14] Longcope and Rackermann: The Relation of Circulating Antibodies to Serum Disease, J. Exper. Med. **27**:341, 1918. Longcope: Antianaphylaxis and Desensitization, Physiol. Rev. **3**:240, 1923.

TESTS FOR PRECIPITIN TO COW'S MILK IN THE BLOOD OF MARASMIC INFANTS

During the last three years, we have conducted investigations on infants with nutritional disorders in order to determine the frequency with which antibodies occur in the blood. In carrying out the precipitin test, we found, as have previous observers, that the use of ordinary milk was exceedingly unsatisfactory owing to the impossibility of obtaining clear solutions. Only very heavy precipitates could be detected. This perhaps explains the negative results obtained by most workers. After various tests, we found that a brand of fat-free dried milk gave almost clear solutions in which slight precipitates could be detected readily. This preparation has been used entirely in our recent tests.

The tests for precipitin to cow's milk were made thus: To 1 c.c. of milk dilutions of 1 : 50, 1 : 100, 1 : 500 and 1 : 1,000 were added 0.1 c.c. and 0.2 c.c. of the serum to be tested.[15] The tests were read after incubation for one hour at 37.5 C.; the tubes were kept on ice for twenty-four hours, and then the final reading was taken. In the earlier tests, controls with normal human serum and normal rabbit or sheep serum were used. These tests were uniformly negative and were later omitted. Positive controls were made by using anti-milk rabbit serum. Controls on the serum of the patient diluted with physiologic sodium chlorid solution and on milk dilutions without the addition of serum were used throughout. The results were recorded as +, + +, + + + and + + + +. When the test showed distinct flocculation, the test was called +. When flocculation was marked, with perhaps a slight gross precipitate deposited on the bottom of the tube, the test was classified as + +. Marked flocculation with a moderate gross deposit in the tube was called + + +; and + + + + was used when the flocculation was extremely marked, with practically all of the protein deposited in the bottom of the tube, leaving a comparatively clear supernatant fluid.

Precipitin tests were made on the blood of ninety-eight marasmic infants. The patients in this group all showed the signs characteristic

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15. All of the dilutions were not used in every test. In some instances, the 1 : 50 or the 1 : 1000 dilution was omitted. Tests with 0.2 c.c. of serum were not made in all cases, owing to the fact that it often seemed unjustifiable to withdraw the larger amount of blood required.

of marasmus. They presented the typical appearance and were greatly under weight. A number had a history of preceding digestive disturbances, usually vomiting or diarrhea. During the period of observation, symptoms were not common. Vomiting or diarrhea occurred in a few; also attacks of upper respiratory infections, common in infants' wards. During the investigation, the infants were fed dilutions of milk or lactic acid milk supplying from 60 to 90 calories a pound.

The precipitin test was positive at some time in eighty of the ninety-eight infants examined. In the positive cases, precipitins were detected in only a small proportion of the total number of tests, but in practically all, the test was at some time from + + to + + + +. Control tests often repeated indicate that precipitins to cow's milk are not present in normal individuals. Tests on nineteen adults or older children were all negative. Blood from twelve new-born infants or infants entirely breast fed were negative. Placental blood from four new-born infants was negative. We have not been able thus far to make control tests on normal, thriving infants, but we have plans for obtaining such material in the near future. Of great value as controls are the numerous negative findings obtained on the patients investigated, and especially those in which there is a disappearance of the precipitin after a period of gain in weight. None of these infants showed any of the usual manifestations of allergy, such as asthma, urticaria or eczema. At previous times, cutaneous tests with milk protein had been made on approximately 100 marasmic infants, with negative results. Such tests were made on twenty-four of the marasmic infants showing marked precipitin reactions, and none of the reactions was positive.

The attempt has been made to correlate the presence of precipitins with the general condition of the patient. As a rule, precipitins to cow's milk protein were absent during the period when the weight was stationary and usually appeared when the weight began to increase. This relationship was not invariable but was true in a sufficient number of cases to suggest strongly that it was real, not merely coincidental. In none of the cases was there any important alteration in the food during the period of stationary weight and the period of weight increase. In the greater number of cases, the food was the same during the two periods. In most cases in which it was possible to conduct observations over a long period of time, it was found that, after a period of gain in weight precipitins disappeared entirely. The relationship between the presence of precipitins and the weight curve is shown in the tabulation of seventeen cases in Table 1.

For purposes of further illustration, ten cases will be discussed.

Tabe 1.—*Relation of the Presence of Precipitin in the Blood of Marasmic Infants to the Gain in Weight*

Case and Age	Date	Precipitins	Food*	Progress Notes
J. G. 1 mo.	11/22/21	...	W. M. dil.	Typical marasmic infant; weight 6¼ lb.
	11/30/21	...	P. M.	Diarrhea; vomiting; food refused
	1/ 2/22	...	W. M. dil.	Improved; stools normal; weight, 6 $^{14}/_{16}$ lb.
	1/25/22	4+	W. L. A. M.	Improved; stools normal; weight, 7 lb.
	2/ 6/22	4+	W. M. dil.	Doing well; stools normal; weight, 7½ lb.
	2/10/22	3+	W. M. dil.	Doing well; weight 7½ lb.
	2/21/22	2+	W. M. dil.	Gaining steadily; weight 8 lb.
	2/27/22	1+	W. M. dil.	Doing well; weight, 8¼ lb.
	3/ 1/22	...	W. M. dil.	Discharged, well; weight, 8½ lb.
M. T. 2 mo.	12/30/21	...	W. M. dil.	Typical marasmic infant; weight, 4$^{10}/_{16}$ lb.
	1/18/22	...	P. M.	Stools loose
	1/25/22	4+	P. M.	Improved; stools normal; weight, 4½ lb.
	2/ 3/22	4+	P. M.	General condition improved; weight climbing daily, 5½ lb.
	2/10/22	0	P. M.	Diarrhea; losing weight rapidly, 4½ lb.
	2/28/22	1+	B. M.	Doing well; gaining slowly, 5 lb.
	3/16/22	2+	W. L. A. M.	Gaining rapidly, 5 $^{11}/_{16}$ lb.
	3/25/22	2+	W. L. A. M.	Gaining rapidly, total of 1 lb. in 2 weeks
	4/14/22	0	W. L. A. M.	Upper respiratory infection; losing weight
	5/10/22	2+	W. L. A. M.	General condition improved; weight, 7 lb.
	5/18/22	2+	W. M. dil.	Doing well; a gain of 11 oz. in 1 week
	5/20/22	...	W. M. dil.	Discharged, well
A. C. 3 wk.	11/29/21	...	W. M. dil.	Typical marasmic; barelip; weight, 6 $^{3}/_{16}$ lb.
	12/24/21	...	W. L. A. M.	Otitis media; refusing food; losing weight
	2/10/22	3+	W. L. A. M.	Doing better; weight, 6 $^{2}/_{16}$ lb.
	2/24/22	4+	W. L. A. M.	Gaining steadily, 6 $^{11}/_{16}$ lb.
	3/ 4/22	3+	W. L. A. M.	Gaining steadily, 7 lb.
	3/16/22	2+	W. L. A. M.	Gaining steadily, 7 $^{13}/_{16}$ lb.
	4/14/22	2+	W. L. A. M.	Doing well; weight, 8 $^{10}/_{16}$ lb.
	4/28/22	2+	W. L. A. M.	Doing well; weight increasing steadily
	5/10/22	1+	W. M. dil.	Gaining steadily, 9 $^{10}/_{16}$ lb.
	5/24/22	0	W. M. dil	Gaining steadily, 10 lb.
	7/ 7/22	0	W. M. dil.	Discharged, well, for operation
A. G. 2 mo.	12/ 2/21	...	W. M. dil.	Typical marasmic infant; harelip; weight, 7½ lb.
	1/ 6/22	...	W. M. dil.	Doing badly; refusing food; vomiting; weight, 6½ lb.
	2/ 6/22	4+	D. M.	General condition improved; weight, 6¾ lb.
	2/10/22	0	P. M.	Diarrhea; losing rapidly, weight, 6¼ lb.
	2/21/22	0	P. M.	General condition improved; stools normal; weight, 6½ lb.
	2/28/22	2+	P. M.	Doing well; gaining; weight, 6 $^{13}/_{16}$ lb.
	3/16/22	2+	W. L. A. M.	Doing well; gaining weight
	4/17/22	3+	W. L. A. M.	Impetigo; weight, 8 lb.
	5/23/22	0	W. L. A. M.	General condition greatly improved; weight, 8½ lb.
	6/15/22	...	W. M. dil.	Discharged
J. T. 6 mo.	4/17/22	3+	W. M. dil.	Typical marasmic infant; weight, 9½ lb.
	4/28/22	2+	W. M. dil.	Doing very well; weight, 9 $^{12}/_{16}$ lb.
	5/ 8/22	2+	B. F.	Doing very well; weight, 10 lb.
	5/24/22	0	B. F.	Doing very well; weight, 10½ lb.
	5/31/22	0	W. M. dil.	Doing very well
	6/ 4/22	...	W. M. dil.	Discharged, well
E. B. 9 mo.	3/10/22	...	W. M. dil	Mild diarrhea prior to admission; weight, 6½ lb.
	4/ 5/22	2+	W. M. dil.	Doing very well; weight, 7¾ lb.
	4/10/22	...	....	Discharged, well
	4/24/22	0	P. M.	Readmitted; diarrhea; weight, 7 lb.
	4/28/22	2+	P. M.	Doing well; stools normal; weight, 6 $^{6}/_{16}$ lb.
	5/12/22	2+	W. M. dil.	Doing well; gaining weight steadily: weight, 7 lb.
R. O. 1 mo.	5/ 5/22	...	W. M. dil.	Marasmic infant; harelip; weight, 6¼ lb.
	5/12/22	3+	W. M. dil.	Doing well; gaining steadily
	5/31/22	1+	D. M.	Doing well; gaining steadily
	7/ 5/22	4+	D. M.	Doing well; weight climbing rapidly
	7/14/22	2+	D. M.	Discharged
R. D. 1 mo.	10/26/22	...	B. M.	Marasmic infant; weight, 5½ lb.
	10/30/22	0	D. M.	Weight stationary
	12/ 2/22	...	P. M.	Diarrhea; dehydrated; weight, 5¼ lb.
	12/24/22	4+	W. L. A. M.	Doing well; weight climbing steadily, 5¾ lb.
	2/ 6/23	4+	W. L. A. M.	Doing well; weight climbing steadily, 7¼ lb.
	2/14/23	...	....	Died of bronchopneumonia
M. R. 2½ mo.	11/19/22	0	W. M.	Marasmic infant; mild diarrhea; weight, 5½ lb.
	1/ 2/23	3+	W. L. A. M.	Doing well; gaining steadily; weight, 6 lb.
	1/ 9/23	3+	W. L. A. M.	Very mild diarrhea
	1/23/23	2+	W. L. A. M.	Doing well; gaining steadily; weight, 6½ lb.
	2/19/23	1+	W. L. A. M.	Doing well; gaining steadily; weight, 8 lb.
	2/26/23	2+	W. M. dil.	Doing well; gaining steadily; weight, 8¼ lb.
	2/28/23	...	W. M. dil.	Discharged, well; weight, 8½ lb.

TABLE 1.—*Relation of the Presence of Precipitin in the Blood of Marasmic Infants to the Gain in Weight—(Continued)*

Case and Age	Date	Precipitins	Food	Progress Notes*
E. W. 1 mo.	11/ 7/22	...	P. M.	Severe malnutrition; mild diarrhea; weight, 8 lb.
	11/28/22	0	P. M.	Diarrhea persists; weight stationary
	1/24/23	2+	W. L. A. M.	Doing well; weight, 9 lb.
A. K. 3 mo.	12/14/22	...	P. M.	Acutely dehydrated; severe malnutrition; weight, 6 lb.
	12/18/22	2+	W. L. A. M.	Doing well; rapid recovery; weight, 6½ lb.
	12/26/22	1+	W. L. A. M.	Doing well; weight, 6 14/16 lb.
	1/ 3/23	3+	W. L. A. M.	Doing very well; weight, 7½ lb.
	1/ 8/23	3+	W. L. A. M.	Doing very well; weight 7 14/16 lb.
	1/17/23	3+	W. L. A. M.	Doing very well; weight, 8 2/16 lb.
	1/26/23	2+	W. L. A. M.	Doing very well; weight, 8 9/16 lb.
	2/ 7/23	2+	W. M. dil.	Doing very well; weight, 9 lb.
	2/13/23	0	W. M. dil.	Doing very well; weight, 9 2/16 lb.
	2/15/23	...	W. M. dil.	Discharged, well
P. A. 2 mo.	2/15/23	...	W. M. dil.	Severe malnutrition; weight, 5 2/16 lb.
	3/ 2/23	1+	W. M. dil.	Doing well; weight, 6 lb.
	3/17/23	2+	W. M. dil.	Doing well except for O. M.; weight, 6 lb.
	3/24/23	2+	W. M. dil.	O. M.; weight stationary
	3/29/23	3+	W. M. dil.	Doing well; weight, 6 6/16 lb.
	4/ 6/23	2+	W. M. dil.	Doing well; weight, 6 9/16 lb.
	4/13/23	3+	W. M. dil.	Doing well; weight, 6 12/16 lb.
	4/24/23	1+	W. M. dil.	Doing well; weight 7¼ lb.; discharged, well
M. R. 1 mo.	2/12/23	...	P. M.	Mild diarrhea prior to admission; weight, 6½ lb.
	2/19/23	0	W. L. A. M.	Stools normal; weight, 6¾ lb.
	2/27/23	0	W. L. A. M.	Diarrhea; losing weight; weight, 6½ lb.
	3/ 8/23	0	W. L. A. M.	Stools normal; general condition improved
	3/17/23	0	P. M.	Diarrhea; weight on decline, 6 lb.
	3/21/23	0	W. L. A. M.	Improved; stools normal
	3/26/23	1+	W. L. A. M.	Doing well; weight, 7 lb.
	4/ 2/23	2+	W. L. A. M.	Doing well; weight, 7¼ lb.
	4/ 5/23	2+	W. L. A. M.	Doing well; weight, 7½ lb.
H. T. 3½ mo.	2/14/23	...	W. M. dil.	Typical marasmic infant; weight, 8¾ lb.
	2/19/23	3+	W. M. dil.	Doing well; weight 8 5/16 lb.
	2/28/23	1+	W. M. dil.	Doing well; weight, 9¾ lb.
	3/ 6/23	1+	W. M. dil.	Doing well; weight 10 lb.
	3/10/23	...	W. M. dil.	Discharged, well; weight, 10¼ lb.
M. W. 2 mo.	9/ 8/22	...	P. M.	Diarrhea; marasmic infant; weight, 7 lb.
	9/12/22	2+	P. M.	Doing well; weight, 7 7/16 lb.
	9/22/22	...	P. M.	Diarrhea; weight, 6 15/16 lb.
	10/14/22	0	P. M.	Doing better; weight stationary, 6 16/16 lb.
	10/31/22	0	P. M.	Weight stationary, 6 11/16 lb.
	11/17/22	2+	W. L. A. M.	Doing well; weight, 7½ lb.
	11/20/22	1+	W. L. A. M.	Doing well
	12/ 4/22	2+	W. L. A. M.	Gaining rapidly; weight, 8 2/16 lb.
	12/21/22	1+	W. L. A. M.	Gaining rapidly; weight, 9¾ lb.
	12/26/22	0	W. L. A. M.	Gaining rapidly; weight, 10 lb.
	12/30/22	...	W. M. dil.	Discharged, well; weight, 10½ lb.
H. M. 3 mo.	2/16/23	...	W. M. dil.	Markedly malnourished; weight, 8 lb.
	2/19/23	0	W. M. dil.	Weight stationary
	2/27/23	0	W. L. A. M.	Weight on decline, 7¾ lb.
	3/ 6/23	0	W. L. A. M.	Weight increasing steadily, 8 lb.
	3/10/23	1+	W. L. A. M.	Weight increasing steadily, 8½ lb.
	3/16/23	0	P. M.	Diarrhea; weight on decline, 8¼ lb.
	3/20/23	0	P. M.	Diarrhea persists
	3/26/23	0	P. M.	Stools normal
	3/31/23	1+	W. L. A. M.	Improving; weight, 8½ lb.
	4/ 4/23	2+	W. L. A. M.	Doing well; weight, 8¼ lb.
	4/10/23	2+	W. L. A. M.	Doing well; weight, 9 lb.
	4/19/22	2+	W. L. A. M.	Doing well; weight, 9 2/16 lb.
	4/24/23	0	W. M. dil.	Doing well; weight, 9¼ lb
	5/ 2/23	0	W. M. dil.	Doing well; weight, 9 6/16 lb.
	5/10/23	0	W. M. dil.	Doing well; weight, 9 16/16 lb.
R. R. 6 wk.	1/ 5/23	2+	W. M. dil.	Typical marasmic; weight, 6 9/16 lb.
	1/11/23	1+	W. M. dil.	Doing well; weight, 6 14/16 lb.
	1/30/23	0	W. M. dil.	Vomiting; weight stationary
	2/22/23	0	W. M. dil.	Weight stationary for 10 days
	2/26/23	0	W. M. dil.	Weight stationary for 2 weeks
	3/ 5/23	1+	W. M. dil.	Gaining steadily; weight, 7 10/16 lb.
	3/10/23	0	W. L. A. M.	Doing poorly; weight stationary
	3/23/23	0	W. L. A. M.	Stools loose; weight, 8 lb.
	3/26/23	0	W. L. A. M.	Stools normal; weight, 7¾ lb.
	3/31/23	1+	W. L. A. M.	Gaining for past 4 days; weight, 8¼ lb.
	4/10/23	1+	W. L. A. M.	Doing well; weight, 8 10/16 lb.
	4/19/23	3+	W. L. A. M.	Doing well; weight, 9 lb.
	5/10/23	1+	W. M. dil.	Doing well; weight, 10 lb.
	5/15/23	0	W. M. dil.	Discharged; weight, 10¼ lb.

* W. M., whole milk; P. M., protein milk; D. M., dried milk; B. M., breast milk; W. L. A. M., whole lactic acid milk; W. M. dil., diluted whole milk; O. M., otitis media.

REPORT OF CASES

Case 1.—A. K., aged 3 months, admitted to the surgical service of the Children's Hospital, October 19, who at birth weighed 7 pounds (3,175 gm.), on admission weighed 6 pounds (2,727 gm.). The patient was operated on for pyloric stenosis, and was discharged, November 3. November 10, the infant was readmitted to the hospital on account of failure to gain and vomiting. In the hospital, diarrhea developed, and the patient was transferred to the medical service, December 14. December 18, the diarrhea had ceased and the precipitin test was strong positive. The results of the subsequent tests are shown in Figure 1.

As indicated by Figure 1, the patient's blood contained precipitin to cow's milk during the period of gain. The precipitin diminished, and at the time of discharge had disappeared entirely. December 28, a guinea-pig was sensitized passively to cow's milk by injection of the patient's blood according to a technic to be described further on.

Case 2.—W. S., aged 3 months, admitted February 19, weighing 7 pounds and 7 ounces (3,373 gm.), at birth weighed 7 pounds (3,175 gm.). The patient had a hare lip and cleft palate. He was never nursed, but was fed on dilutions ot whole milk from birth. He manifested all the signs of marasmus. Figure 2 gives the data of importance.

As shown in Figure 2, the patient gained very rapidly and the blood contained very marked precipitin to cow's milk. February 25, a positive Dale test was obtained from the uterus of a guinea-pig which had been injected with the patient's blood on the previous day. Just before the patient's discharge, the precipitin had diminished. The gain in weight continued steadily, and, May 16, the precipitin reaction was negative.

Case 3.—F. S., aged 7 weeks, admitted, November 10, weighed 5 pounds and 4 ounces (2,371 gm.) at birth. He was breast fed entirely for one week and was then given mixed feedings. There was no history of diarrhea, but there was occasionally vomiting. The infant was very emaciated, weighing 5 pounds and 9 ounces (2,493 gm.)

The important data are shown in Figure 3. During the period of stationary weight, precipitin to cow's milk was absent from the blood. When the weight began to increase, precipitins were present.

Case 4.—D. L., aged 2 months, admitted, March 21, weighing 4 pounds and 10 ounces (2,098 gm.), was never breast fed, but was given dilutions of whole milk from birth. The infant did not gain in weight, presenting a picture of extreme malnutrition.

The weight curve (Fig. 4) shows that the blood contained precipitin during the period of rapid gain. April 25, precipitins were absent.

Case 5.—D. M., aged 3 months, admitted, February 14, weighing 4 pounds and 15 ounces (2,240 gm.), at birth weighed 5½ pounds (1,495 gm.). The infant was breast fed until admission. It nursed well but did not gain, was extremely malnourished and presented the usual picture of marasmus.

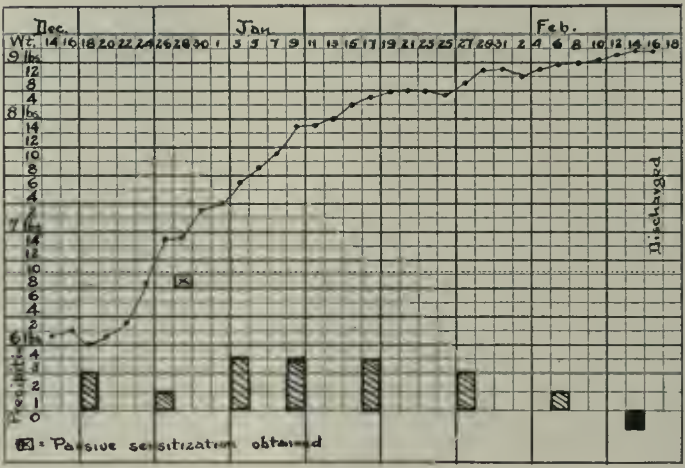

Fig. 1 (Case 1).—Precipitins were present during the period of rapid gain in weight, and disappeared with continued improvement.

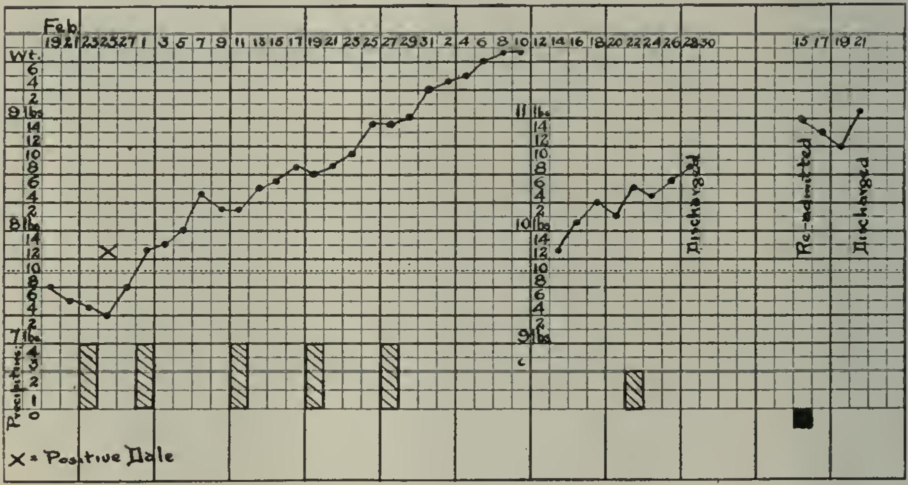

Fig. 2 (Case 2).—Precipitins were present during the period of rapid gain in weight, and disappeared with continued improvement. A record of the Dale test is shown in Figure 17.

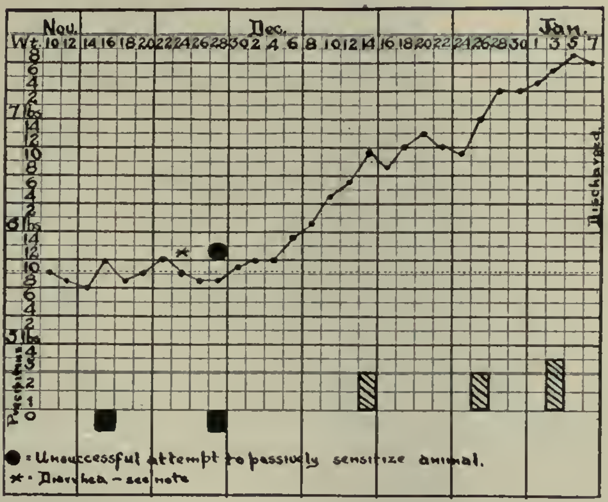

Fig. 3 (Case 3).—Precipitins were absent during the period of stationary weight and subsequently appeared, coincidently with gain in weight.

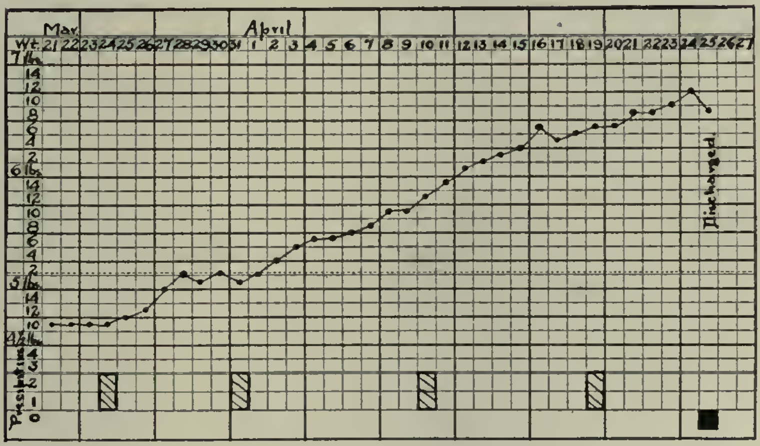

Fig. 4 (Case 4).—Precipitins were present during the period of gain in weight and disappeared with continued improvement.

Figure 5 shows the absence of precipitins during the period of stationary weight, and their presence when the weight began to increase. Later, the precipitins diminished and then disappeared, but were again present, April 25.

Case 6.—J. T., aged 6 months, admitted, April 17, weighing 9 pounds and 6 ounces (4,252 gm.), was breast fed for three months, and was then given a whole milk dilution, whereupon vomiting and loss of weight occurred. He was then fed undiluted whole milk, with continuation of the symptoms. The state of nourishment was extremely poor. The infant was then fed dilutions of whole milk. The weight curve is shown in Figure 6. Precipitins were present in the blood at first, and later disappeared.

A point of special interest illustrated by this case is the close correspondence between the precipitin tests and the anaphylactic tests.

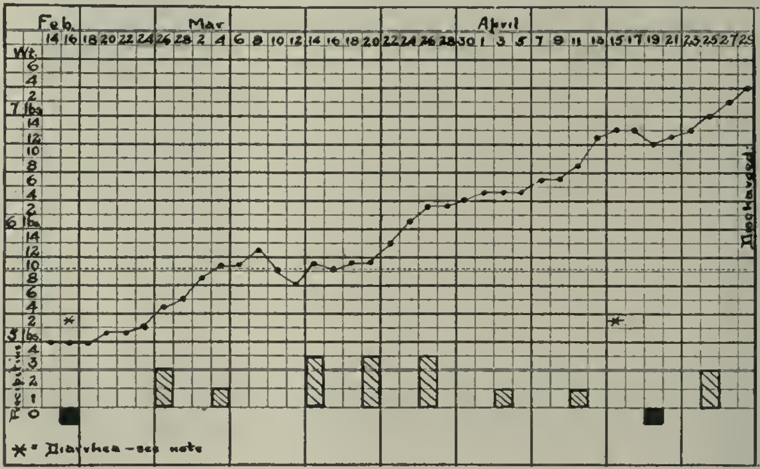

Fig. 5 (Case 5).—Precipitins were absent during the period of stationary weight, also in the course of an intercurrent diarrhea. Antibody appeared subsequently when the child was gaining in weight.

At the times the blood contained precipitins, it was possible passively to sensitize guinea-pigs by injections of the patient's blood. On the two occasions when the blood contained no precipitins passive sensitization experiments were negative.

Case 7.—S. N., aged 1 day, admitted, February 26, was afflicted with a hare lip and cleft palate. The weight was 7 pounds and 9 ounces (3,430 gm.) Until March 12, the infant was fed human milk entirely, on which date she was given one feeding of diluted cow's milk. On breast milk two precipitin tests were entirely negative, and a third test six days after beginning cow's milk was also negative. As shown in Figure 7, the gain in weight on cow's milk was accompanied by the development of precipitins to cow's milk in the patient's blood.

Case 8.—B. K., aged 22 days, admitted, March 3, weighing 5 pounds and 3 ounces (2,353 gm.), was premature, weighing 5 pounds and 12 ounces (2,608

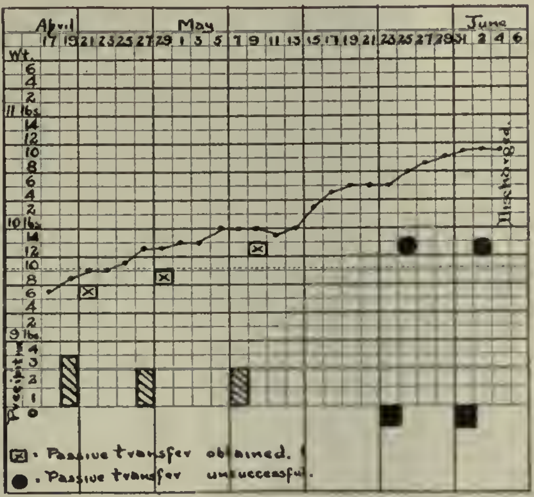

Fig. 6 (Case 6).—Relationship between the presence of precipitins and gain in weight; disappearance of reaction bodies with continued improvement. This chart illustrates further the parallelism between the precipitin tests and animal experiments.

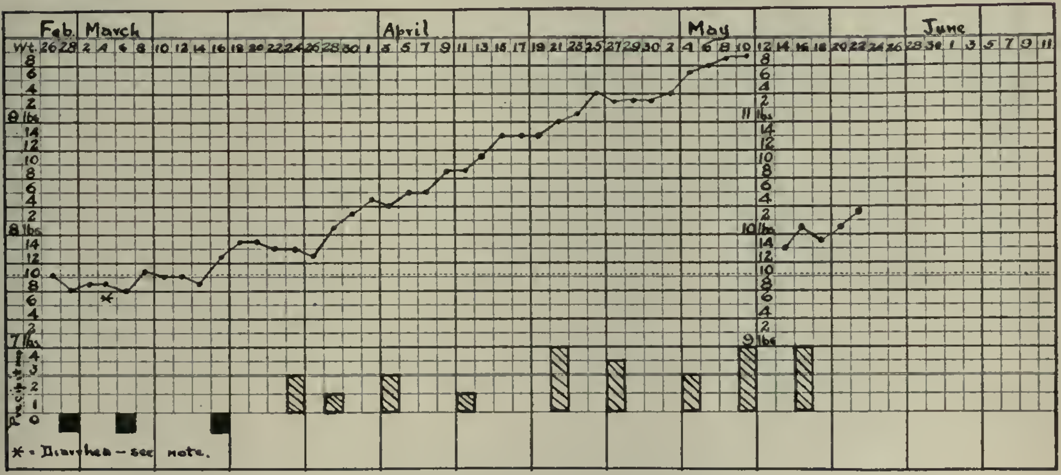

Fig. 7 (Case 7).—Precipitins were absent during the period of stationary weight and appeared when the child was gaining weight.

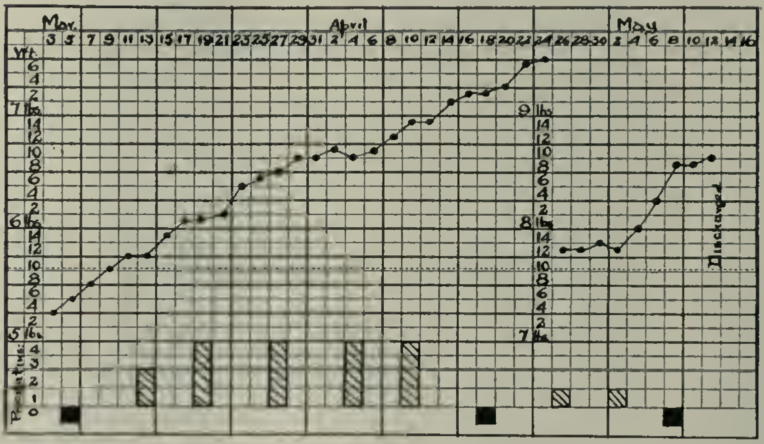

Fig. 8. (Case 8).—Relationship of precipitin to gain in weight; disappearance of precipitin with continued improvement.

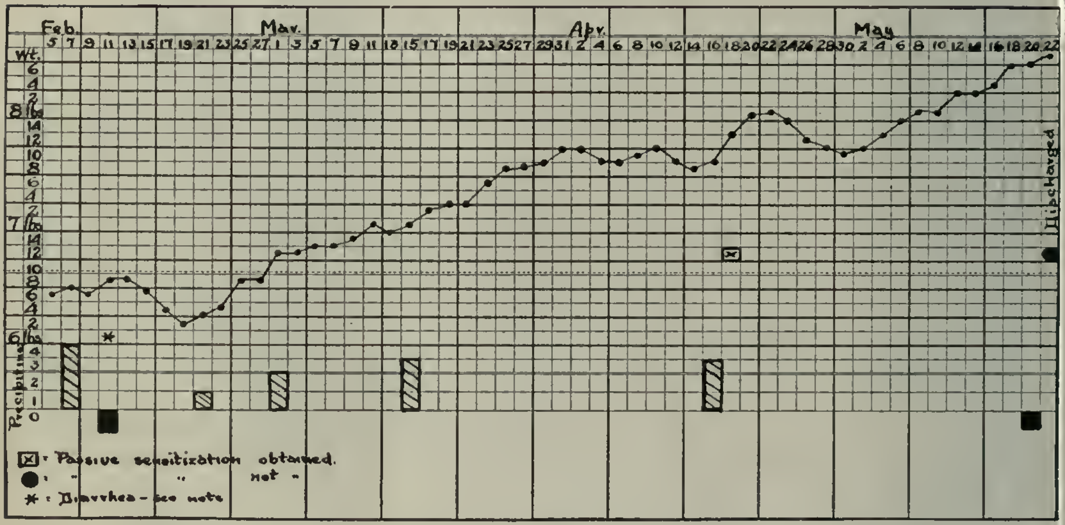

Fig. 9 (Case 9).—Precipitins were present during the period of gain; disappeared during diarrhea, and reappeared coincident with recovery and further gain in weight.

gm.) at birth. He had never been breast fed, and was very emaciated, but thrived on a whole milk dilution. The data are shown in Figure 8. On admission, the blood contained no precipitin. Subsequently, precipitins appeared, then diminished and finally disappeared.

Case 9.—A. G., aged 2 months, admitted, February 5, weighing 6 pounds and 6 ounces (2,898 gm.), had never been breast fed but had been given formulas made from dilutions of whole milk. She had a cleft palate and a hare lip. Feeding had been difficult, and was complicated by refusal of food and vomiting. Emaciation was marked, with the usual signs of marasmus. The data are given in Figure 9.

The disappearance of precipitins from the blood of this patient during diarrhea is shown by the test on February 11. This has been practically a constant finding whenever diarrhea has occurred in a patient under investigation. Its significance will be discussed in a later communication. April 18, a passive sensitization test was positive. Figure 9 further illustrates the disappearance of the precipitins, at which time a passive sensitization test was negative.

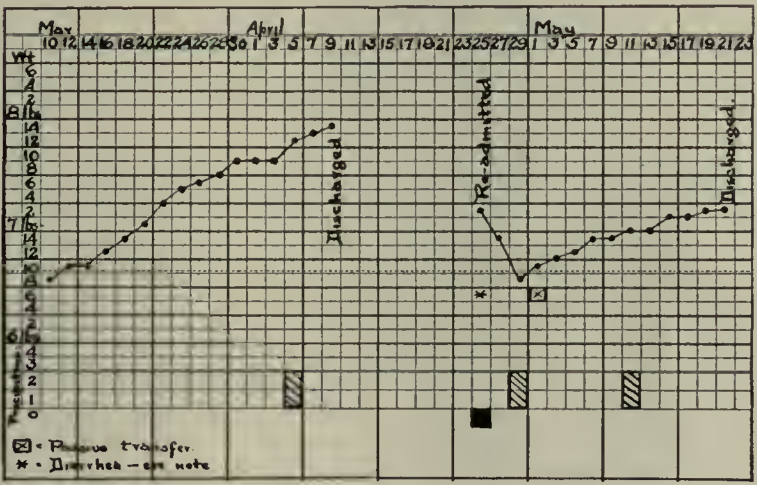

Fig. 10 (Case 10).—Relationship between precipitin and gain in weight. In this case, as in Cases 3, 5 and 9, the precipitins were absent during an intercurrent attack of diarrhea and reappeared with recovery and gain in weight.

Case 10.—E. B., aged 9 months, on admission, March 10, weighed 6 pounds and 8 ounces (2,954 gm.). The baby was breast fed for two months, at which time it was given dilutions of whole milk. It did not gain and developed mild diarrhea, but did well when given a diluted whole milk feeding. April 5, the blood showed the presence of precipitins to cow's milk, but no cow's milk protein. The infant was discharged from the hospital, April 9. April 23, it was readmitted because of diarrhea of one week's duration. It was in fair condition but had lost 10 ounces (283 gm.) since discharge from the hospital. At the time of admission, the blood showed no milk protein and no precipitin for cow's milk. Two days later, after diarrhea had ceased, the blood contained precipitin. Data are given in Figure 10.

The results cited demonstrate that the blood of a large number of marasmic infants contains precipitin for cow's milk. From immunologic data, it seems well established that specific precipitins to protein represent a response on the part of organisms to the entrance of foreign protein into the body fluids. On this basis, it would seem safe to assume that, in marasmic infants receiving cow's milk, undigested or partly digested protein had been absorbed, and, entering the blood, caused the production of precipitins.

TESTS FOR ANAPHYLACTIC ANTIBODY IN THE BLOOD OF MARASMIC INFANTS

Blood containing precipitin to a foreign protein is often capable of passively sensitizing to that protein another animal of the same or related species. In other words, the antibody causing precipitation and the anaphylactic antibody are either identical or usually occur in association. There has been considerable discussion concerning the identity or nonidentity of the anaphylactic and the precipitating antibody, which we shall not enter at this time.[16]

Owing to the marked precipitin formation observed in marasmic infants, it seemed of interest and importance to ascertain whether the blood containing precipitin would passively sensitize guinea-pigs to cow's milk protein. Tests were made by injecting into a guinea-pig, intraperitoneally, from 2 to 5 c.c. of the blood to be tested, and twenty-four hours later giving the animal from 0.25 to 1 c.c. of milk by intravenous injection. If the injected blood contained the anaphylactic antibody in sufficient amount, one might expect the treated animal to develop symptoms of anaphylactic shock.

Thirty such tests were made, the blood from marasmic infants showing marked precipitin formation being employed. In fourteen instances, the animal developed severe symptoms of anaphylactic shock. In four tests, the animals developed symptoms suggestive of anaphylactic shock, but not of sufficient severity to be considered unequivocal. The disturbances shown by the first mentioned animals were typical, and death within five minutes occurred in nine. The other animals developed severe symptoms, but recovered gradually in the manner usual in nonfatal anaphylactic shock. The postmortem examination on the animals dying of anaphylactic shock and those sacrificed during severe shock revealed the characteristic distension of the lungs.

It has been shown by a number of observers that the intravenous injection of various substances may cause symptoms in guinea-pigs which are practically identical with those of anaphylactic shock. Karsner and Hanslik and Wetterman[17] have shown that this anaphylactoid reaction is due to pulmonary thrombosis. In recognition of the possibility that we were dealing with this type of reaction, the lungs of a number of the animals were examined for the presence of thrombi, but with entirely negative results. Our observations were also carefully controlled. The amount of milk given by intravenous injection caused no symptoms when administered to normal guinea-pigs or to those previously treated with normal human blood. Further control of data of importance are furnished by thirty-seven tests in which blood not containing precipitin was used. In none of these did the blood passively sensitize a guinea-pig to cow's milk.

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[16] The literature has recently been reviewd by Longcope (Footnote 4, second reference) and by Wells: Physiol. Rev. **1**:44, 1921.

It, therefore, seems established that the blood of marasmic infants not only contains precipitin for cow's milk but also may be capable of passively sensitizing guinea-pigs to cow's milk.

Probably the most clear-cut evidence of anaphylaxis obtainable at present is to be had by means of the method of Dale. Schultz found that the intestine of a sensitized guinea-pig contracted markedly when brought into contact with the antigen to which the animal was sensitized. Dale[18] elaborated the method and used the uterus of a virgin guinea-pig. By this means, a graphic record of the uterine contraction could be recorded on a smoked drum by a lever attached to the uterine horn.

Our tests were made by giving a female guinea-pig an intraperitoneal injection of from 2.5 to 5 c.c. of the blood to be investigated.[19] Twenty-four hours later, the animal was killed; and one of the uterine horns was immersed in oxygenated Locke's solution and connected with a lever writing on a smoked drum revolving very slowly. When the uterus assumed a regular rate of contraction, 0.25 c.c. of milk was added to the Locke's solution. In four instances, the blood of infants containing precipitin to cow's milk passively sensitized guinea-pigs sufficiently to give a positive Dale test. Three of the records are shown in Figures 12, 13 and 14. In Figure 11 a positive control is shown. The guinea-pig had received an injection of 2 c.c. of anti-milk rabbit serum twenty-four hours before the test. The record shows the uterine contraction after the addition of 0.25 c.c. of milk to the Locke's solution in which the uterus was immersed. In all of these experiments, the uterine contraction was complete. These tests have been adequatedly controlled. The addition of 0.25 c.c. of milk will not cause the contraction of the uterine horn of an untreated

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[17] Karsner and Hanslik: Further Observations on Anaphylactoid Phenomena from Various Agents, Including Histamine, Proc. Soc. Exper. Biol. & Med. **19**:302, 1922; Anaphylactoid Phenomena from the Intravenous Administration of Various Colloids, etc., J. Pharmacol. & Exper. Therap. **14**:379 (Jan.) 1920; Effects of Various Colloids and Other Agents on Bronchi or Perfused Lungs, J. Pharmacol. & Exper. Therap. **14**:449 (Feb.) 1920. Hanzlik, Karsner and Wetterman: Anaphylactoid Phenomena from Thromboplastic Agents, J Pharmacol. & Exper. Therap. **14**:229 (Nov.) 1919.

[18] Dale: J. Pharmacol. & Exper. Therap. **4**:167, 1913.

[19] Recently, we have used from 2 to 3 c.c. of inactivated serum for this purpose.

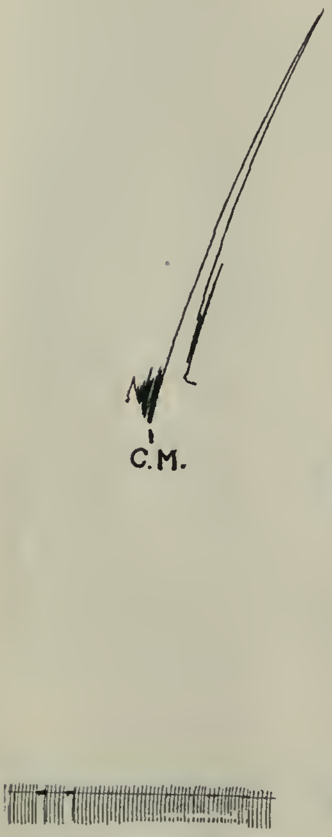

Figure 11

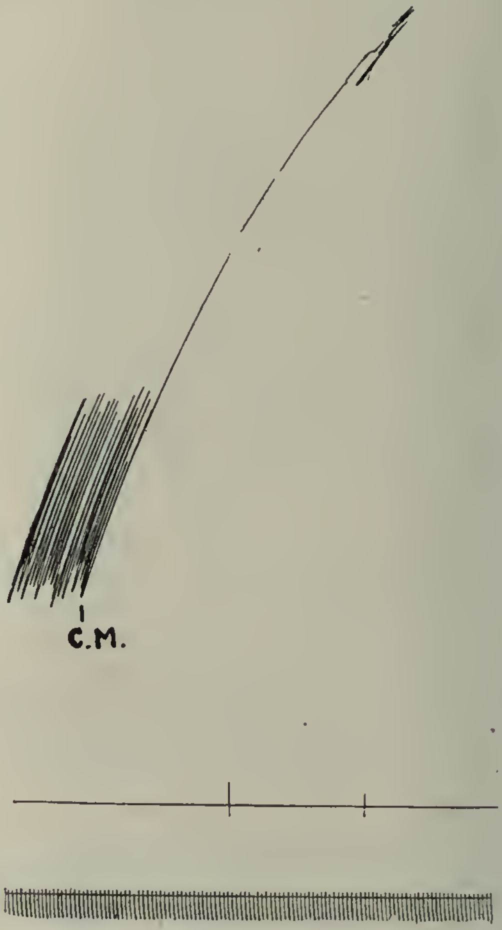

Figure 12

Fig. 11 (Case 11).—Positive Dale test (control). A guinea-pig was passively sensitized by an injection of 2 c.c. of anti-milk rabbit serum; 0.25 c.c. of milk (0.012 gm. of casein) added at the point designated *C.M.* produced complete contraction. The time is indicated in minutes.

Fig. 12 (Case R. D.).—Positive Dale test. A guinea-pig was passively sensitized by an injection of 3.5 c.c. of citrated blood; 0.25 c.c. of milk (0.012 gm. of casein) added at point designated *C.M.* produced complete contraction. Precipitins were 4 plus. The time is indicated in minutes.

guinea-pig. During the course of these observations, we have obtained controls showing that normal human blood will not sensitize the uterus of a guinea-pig to cow's milk.

THE ABSORPTION OF UNDIGESTED OR PARTIALLY DIGESTED PROTEIN

A question which is fundamental to a proper appreciation of the whole process concerns the factors which determine the passage of

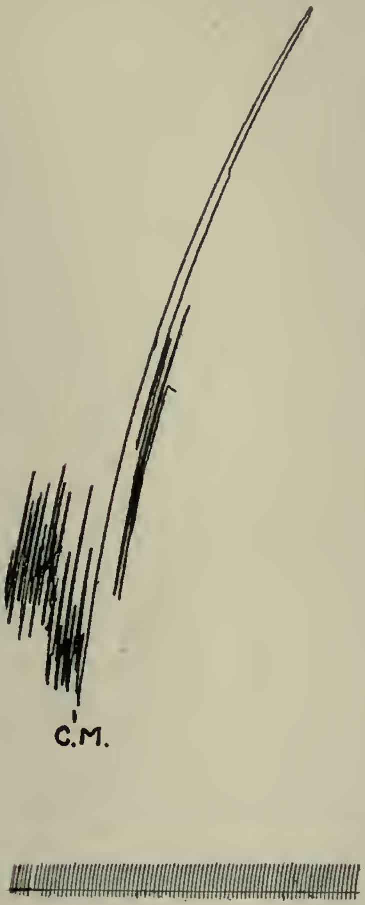

Figure 13

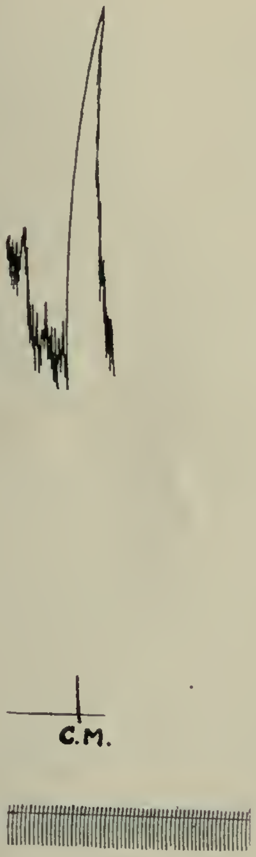

Figure 14

Fig. 13 (Case W. S.).—Positive Dale test. A guinea-pig was passively sensitized by an injection of 4 c.c. of citrated blood; 0.25 c.c. of milk (0.012 gm. of casein) added at point designated *C.M.* produced complete contraction. Precipitins were 4 plus. The time is indicated in minutes.

Fig. 14 (Case B. C.).—Positive Dale test. A guinea-pig was passively sensitized by an injection of 2.5 c.c. of serum (inactivated by incubation at 56 C. for one hour); 0.25 c.c. of milk (0.012 gm. of casein) added at point designated *C.M.* produced complete contraction. Precipitins were 4 plus. The time is indicated in minutes.

antigenic protein through the intestinal wall. Is this of frequent occurrence in young infants, or is it due to some abnormality of intestinal structure of function? The data available at present are insufficient to enable us to discuss the question with assurance, particularly in reference to the first mentioned possibility. This phase of the problem is at the present time under investigation, to which it is well adapted. Concerning the passage under abnormal conditions of unaltered protein or of protein with antigenic properties, we have some data of importance. Lust, Schloss and Worthen and others have observed that in diarrhea the intestine is apt to be permeable to antigenic protein. Certain data obtained in the present investigation confirm these earlier results. The blood of infants with diarrhea was examined by means of the precipitin test, and also by means of the anaphylactic test, for the presence of milk protein. The precipitin test was carried out by diluting 0.1 c.c. and 0.2 c.c. of the patient's blood serum to 1 c.c. with physiologic sodium chlorid solution and adding to this 0.1 c.c. of anti-milk rabbit serum of a titer above 1 : 1,000. The tubes were incubated and read in the same manner as in the tests for antibody described previously. Controls were made of the patient's serum similarly diluted, but with the addition of normal rabbit serum and of 1 : 10 and 2 : 10 dilutions of normal human serum with the addition of 0.1 c.c. of anti-milk rabbit serum.

The anaphylactic tests were carried out by injecting from 2 to 5 c.c. of citrated blood into the peritoneal cavity of a guinea-pig and, giving after an interval of from nineteen to twenty-one days, an intravenous injection of from 0.25 to 1 c.c. of milk. If the blood contained cow's milk protein, it might be expected that the guinea-pig would become sensitized so that an injection of milk at the end of three weeks would cause anaphylactic shock. Precipitin tests for cow's milk protein were made in thirty-three cases of severe diarrhea, with positive results in eight. During the course of the investigation, precipitin tests for cow's milk protein (antigen) were made on thirty marasmic infants. All of these tests were negative, indicating that the amount of cow's milk protein detectable by our technic does not appear in the blood stream of these patients.[20] These cases serve as negative controls.

The anaphylactic test for milk protein was carried out in thirty-three cases of severe diarrhea. The results were positive in seventeen cases and negative in sixteen. The animals developed severe and unquestionable symptoms. Five of the animals died within five minutes and showed typical signs on postmortem examination. For the purpose of detecting antigen in the blood, it seems that the anaphylactic test was more delicate than the precipitin test as we performed it. As a rule, in the cases showing a positive precipitin reaction, the anaphylactic test was also positive. There was only one exception. These results show that, in at least a considerable number of cases of diarrhea, milk protein passes through the intestinal wall and enters the blood and body fluids.

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[20] In order to obtain serum sufficiently free from turbidity, it is necessary to obtain the blood after a fast of eight hours. It seems possible that, if a small amount of protein were absorbed in an unaltered form, it might become so diminished in this time that it could not be detected. The same would seem to apply to the cases of diarrhea. These patients were not fasted intentionally, but many refused food or vomited or had been given no milk for several hours.

THE APPEARANCE OF PRECIPITIN TO COW'S MILK IN THE BLOOD FOLLOWING THE ABSORPTION OF ANTIGENIC PROTEIN

It seems of importance to determine, if possible, whether the milk protein absorbed during diarrhea causes the appearance of antibodies. If this is true, it may offer an explanation for the presence of antibodies in some cases of marasmus. In marasmic infants, there is not infrequently a history of diarrhea, and at times there are recurring attacks. We have some data which bear directly on this question. Observations in seventeen cases of diarrhea showed no precipitin during the attack, and precipitins were present in all from ten to fourteen days after the diarrhea had subsided. Tests for milk protein in the patient's blood were made during the diarrhea in thirteen of these cases. The results were positive in eight cases, questionable in three, and negative in two. At the time the blood contained precipitin for cow's milk, the attempt was made passively to sensitize guinea-pigs by injections of the patient's blood. The results were positive in five cases.

Four cases in which it was possible to demonstrate the presence of milk protein in the blood during diarrhea and later to detect the presence of precipitins will be cited in illustration.

Case 11—A. D., aged 6 months, admitted, August 9, weighing 7 pounds and 6 ounces (3,345 gm.), had had diarrhea of fourteen days' duration. The stools were green and watery. The feedings since birth had been dilutions of whole milk. The infant on admission was very poorly nourished and dehydrated, with toxic symptoms. On admission, the blood contained milk protein, but no precipitin to cow's milk. The diarrhea improved, and about a month later the blood contained precipitin to cow's milk. Data are given in Figure 15.

Case 12.—A. M., aged 2 months, admitted, March 13, weighing 8 pounds and 3 ounces (3,714 gm.), at birth weighed 8 pounds (3,629 gm.). The patient had been breast fed for one month and was then given feedings of diluted whole milk in addition. Three days before admission, diarrhea developed, accompanied by vomiting, refusal of food and convulsions. On admission, there was marked dehydration. Data are given in Figure 16.

On admission, the blood (Case 12, Fig. 16) contained no precipitin, but did show antigen by the precipitin test. The latter result was confirmed by an anaphylactic test. Eleven days after the positive antigen test, the blood showed precipitin to cow's milk.

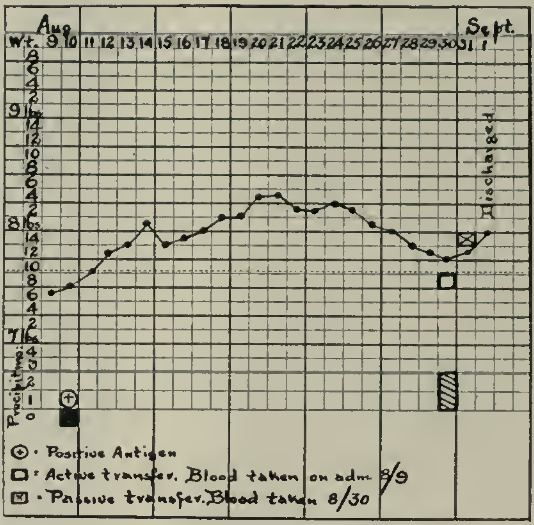

Fig. 15 (Case 11).—Precipitin was absent and antigen present, the latter being confirmed by animal experiment, during severe diarrhea with dehydration and pronounced toxic signs. There was development of precipitin two weeks later, coincident with recovery and gain in weight.

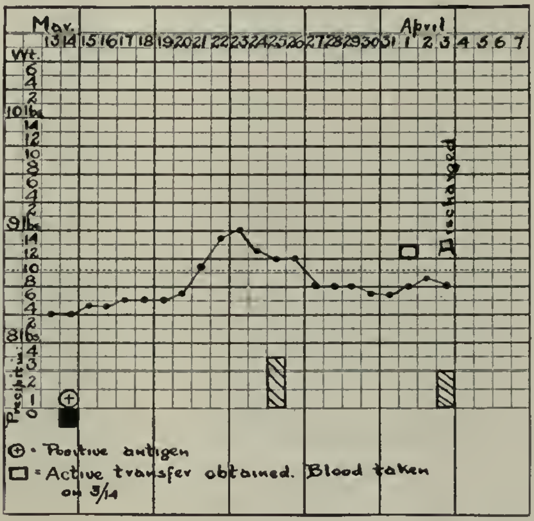

Fig. 16 (Case 12).—Precipitin was absent and antigen present during severe diarrhea. Precipitin appeared eleven days later, coincidently with recovery. In this case, the antigen test was confirmed by animal experiment.

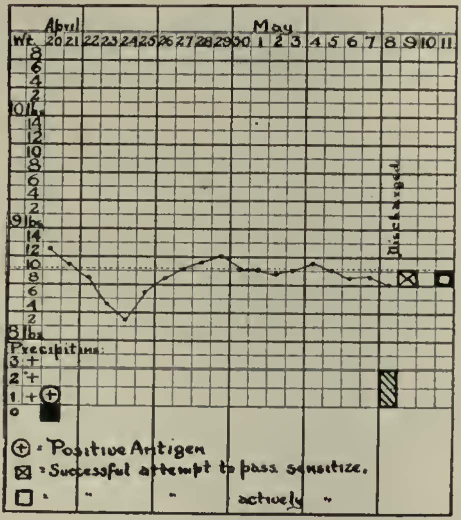

Fig. 17 (Case 13).—Precipitin was absent and antigen present during severe diarrhea. Precipitin appeared eighteen days later. In this case, both the antigen tests on admission and the precipitin tests at the time of discharge were confirmed by animal experiments.

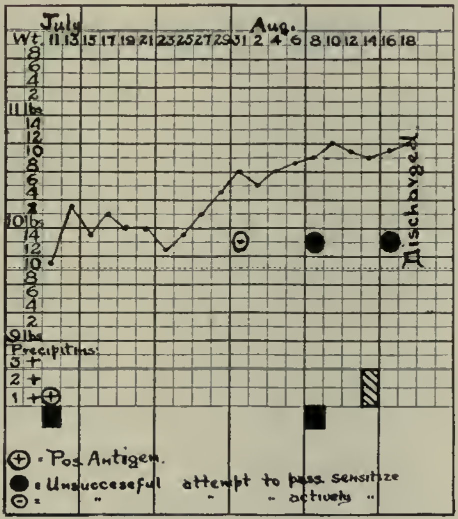

Fig. 18 (Case 14).—Precipitin was absent and antigen present during severe diarrhea. This case was the only one in which the finding of antigen was not confirmed by animal experiments.

CASE 13.—M. H., aged 3 months, admitted, April 20, weighing 8 pounds and 12 ounces (3,969 gm.), at birth weighed 8 pounds (3,629 gm.). The infant was breast fed for two weeks, then given whole milk dilution. Three days before admission, diarrhea developed, accompanied by vomiting and refusal of food. The infant was in poor condition, and was dehydrated and toxic. Data are given in Figure 17.

On admission, the blood showed the presence of milk protein by the precipitin test. This was confirmed by injecting the patient's blood into a guinea-pig, which developed anaphylactic shock three weeks later when given an injection of milk. Antibody (precipitin) to cow's milk was absent on admission, but was present on examination eighteen days later. This case illustrates the presence of antigen and absence of antibody.

CASE 14.—F. G., aged 7 months, admitted, July 11, weighing 9 pounds and 10 ounces (4,366 gm.), was breast fed three months and was then given diluted milk. One week prior to admission, it refused food; vomited, and developed diarrhea. The stools were loose and green, and the patient was acutely ill on admission.

As shown by Figure 18, this patient's blood contained antigen but no antibody on admission. Seventeen days later, the blood contained precipitin to cow's milk.

COMMENT

The results cited in this communication justify the belief that the blood of most marasmic infants contains precipitin to cow's milk. In many cases, the blood of the patient has the property of passively sensitizing guinea-pigs to cow's milk, thus demonstrating the presence also of the anaphylactic antibody. A question which we should like to answer is whether the entrance of foreign protein into the blood stream bears any causative relationship to the nutritional disorder. We do not feel that we have at the present time sufficient data to discuss this question with assurance or to estimate the practical importance of the presence of precipitin to cow's milk in the blood of marasmic infants. To speculate briefly on the subject is not unwarranted.

It is generally believed that the occurrence in the blood of precipitin for protein represents a protective reaction elicited by the entrance of foreign protein into the blood stream. In experimental animals, repeated injections of foreign protein cause the formation of precipitin for that protein; and after the injections are suspended, the precipitin gradually disappears. Of special interest are the observations derived from anaphylactic experiments on guinea-pigs. When the sensitization is greatest, there is little or no precipitin in the circulating blood. When precipitin appears, the animal is relatively insensitive, although its blood is capable of passively sensitizing another animal.[21] This is quite in accord with the cellular theory of anaphylaxis (Dale). It is a suggestive fact that marasmic infants are apt to show precipitin to cow's milk in their blood only at the time when they begin to gain in weight, and that after a period of gain, the precipitin disappears. During the period when the infant fails to gain, foreign protein may be entering the blood stream in sufficient amounts to cause disturbances. This protein may cause the gradual production of precipitin, which, when produced in sufficient amount, will eliminate the effect of the foreign protein. A gain in weight then ensues. With the improvement in the patient's general condition, the intestinal tract becomes impermeable to undigested or incompletely digested protein and the precipitin disappears from the blood.[22] To put this hypothesis on a substantial basis, it would be necessary to show in many individual cases that foreign protein is absorbed by marasmic infants during the period of stationary weight and that the subsequent appearance of precipitin is correlated closely with the clinical improvement of the patient. Part of this evidence is available, but as yet we have not demonstrated directly the absorption of foreign protein during the acute stage of marasmus, although the results of previous work indicate that such absorption is likely to occur.[23] Moreover, the presence of precipitin to cow's milk protein in the blood of marasmic infants almost certainly indicates that cow's milk protein with antigenic properties has entered the blood stream at some time. We have shown directly, however, that foreign protein is absorbed during diarrhea, and that such absorption is followed by the appearance of precipitin and the anaphylactic antibody. In some cases of marasmus, the development of antibodies in the blood may follow a previous attack of diarrhea. It is possible that therapeutic tests may give useful evidence bearing on the clinical importance of the absorption of antigenic protein by marasmic infants.

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[21] Wells, H. G.: The Present Status of the Problems of Anaphylaxis, Physiol. Rev. **1**:44 (Jan.) 1921.

We have put forth this hypothesis mainly to illustrate that it is not impossible that the absorption of foreign protein may play a rôle in the causation of marasmus. This view is in accord with many clinical observations.

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[22] There is another interpretation for these data. It is possible that a small amount of precipitin may be present during the period of stationary weight, but is not detected owing to its rapid combination with the foreign protein which is absorbed from the bowel and in this way is removed from the blood. Also it is possible that the detection of precipitin during the period of gain may not be due to its appearance at this time but to the fact that the intestine no longer permits the passage of milk protein. In this event, the precipitin, which rapidly combined with the foreign protein during the period of stationary weight, would now be free in the blood and readily detectable by the precipitin test.

[23] The failure to demonstrate antigen in cases of marasmus may be due to the fact that the antigen is rapidly combined with precipitin and thus removed from the blood as quickly as it is absorbed (compare Footnote 20).

It is conceivable, on the other hand, that the presence in the blood of marasmic infants of reaction bodies to cow's milk protein may be merely indicative of the incidental entrance of cow's milk protein into the blood stream owing to a temporary change in the intestine and may have no special etiologic significance. Fortunately, this problem is admirably adapted to investigation, which we are conducting at the present time.

SUMMARY

The blood of ninety-eight marasmic infants was examined by a special technic for precipitin to cow's milk. The test was positive in eighty subjects. Precipitin was not present in the blood at all times, but in some cases it was found in only a relatively small number out of the total examinations.

The attempt was made passively to sensitize guinea-pigs to cow's milk by the injection of the blood of marasmic infants which contained precipitin. Thirty such tests were made. Fourteen were positive, four doubtful and twelve negative. In four cases it was possible to obtain evidence of passive sensitization by means of the technic of Dale.

During the course of diarrhea, it was possible to demonstrate the absorption of antigenic cow's milk protein, and later to observe the appearance of precipitin to cow's milk in the blood.

125 East Seventy-Second Street.

HYDROGEN-ION CONCENTRATION OF GASTRIC CONTENTS OF INFANTS *

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Artificially fed infants produce only a small amount of hydrochloric acid during digestion. The amount is not sufficient to show free hydrochloric acid, but brings the stomach contents to a hydrogen-ion concentration of, roughly, 1×10^{-5}, or p_H 5.0. The present study was undertaken to secure data on the p_H of the gastric contents of infants; to discover the normal range on a given standard meal, and to determine the factors which cause the variations of acidity: (1) digestion time, (2) previous type of feeding, (3) the child's age, (4) the amount of test meal and (5) the concentration. Without this information, we have no basis for the interpretation of the findings of gastric analysis in pathologic conditions in infants. Work of this nature has recently been reported by Davidsohn,[1] who has reviewed the literature and has also studied some of the factors in gastric physiology.

This study deals only with the hydrogen-ion concentration of gastric contents removed after a test meal. Other aspects of the problem are at present under investigation. Attempt was made to simulate the normal conditions. Therefore, a test meal of milk was merely substituted for a regular feeding; usually, at 10 a. m., when the child's last feeding had been at 6 a. m.

METHOD

The Test Meal.—A milk meal was desired, and a powdered milk preparation, dissolved in distilled water, was selected because its composition remained constant and its concentration might be varied at will and was accurately known. The composition is as follows: fat, 12 per cent.; lactose, 46; protein, 32; salts, 7; moisture, 3.

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* Received for publication, Sept. 10, 1923.

* From the Department of Pediatrics, Yale University School of Medicine.

* Work done in this paper was taken in part from the theses submitted by Drs. Johnston and Haskins for the degree of Doctor of Medicine, Yale University.

[1] Davidsohn, H.: Neuere Arbeiten zur Physiologie u. Pathologie der Magenverdauung beim Säugling, Arch. f. Kinderh. **69**:142-155 (April) 1921; Beitrag zur Physiologie u. Pathologie der Magenverdauung beim Säugling, ibid. **69**:239-244 (April) 1921.

The concentration eight parts of powdered milk to 100 parts of water was given because it corresponds approximately to skim milk. The concentration was doubled and halved, and the results of these changes will be considered. What is referred to later, however, as the "standard meal" is in all cases powdered milk eight parts to water 100 parts.

The p_H of this meal as determined colorimetrically from a dialyzate and by the hydrogen electrode was 6.2. What the figures for the p_H represent in terms of tenth-normal hydrochloric acid may be estimated roughly from the following data on the buffer value of this meal: 25 c.c. of tenth-normal hydrochloric acid added to a 100 c.c. meal changes p_H 6.2 to p_H 5.6; 50 c.c. of tenth-normal hydrochloric acid added to a 100 c.c. meal changes p_H 6.2 to p_H 4.8; 80 c.c. of tenth-normal hydrochloric acid added to a 100 c.c. meal changes p_H 6.2 to p_H 3.5. These values cannot be applied directly to stomach contents, because of the interference of undetermined factors, regurgitation, secretion, etc.; but they may be considered useful approximations of the acid value represented by the p_H.

The data obtained are not directly comparable to those in the literature obtained after the subject has been fasting and has then been fed a meal such as toast and tea. The use of a milk meal involves the feeding of a large amount of buffer, so that the values for the acidity may seem very low compared to those on a test meal with a small amount of buffer. The values are considered to represent the physiologic reaction of the stomach to a normal meal.

The advantages of this meal over others used in the literature are: (1) its constancy and reproducibility—the p_H and buffer values are known and do not vary from sample to sample as with milk not dried; (2) its low fat values, which cause less digestive difficulty and cause more marked differences in the acidity and motility than whole milk.

Technic of Obtaining Samples.—With infants fed on a three or four hour schedule, the regular meal was omitted and a test meal substituted. Since the psychic elements may play a considerable part, we made an effort to have the babies as quiet as possible. They were not disturbed during the digestive period. The amount of the meal was made to correspond roughly to the amount of feeding the child normally received, and was 100, 150 or 200 c.c. The estimation of the digestive interval was made by taking the mean time of the feeding interval as the starting point. When vomiting or refusal of feeding occurred, the amount vomited or refused was estimated. In a few instances, it was necessary to resort to feeding by gavage.

At a given interval thereafter, a rubber tube was passed into the stomach. In most cases, this resulted in the expulsion through the lumen of the tube of a considerable portion of the gastric contents.

The remainder was removed by suction secured by the use of a Dakin syringe inserted into the free end of the tube. The amount recovered was measured.

In the withdrawal of small portions of contents for a study of the influence of digestive time on the p_H, a nasal catheter was sometimes passed, and kept in place during the entire period, samples being withdrawn at intervals by suction. It seemed to make no difference whether this method were used or whether a separate introduction of the tube were made for each sample.

All apparatus was boiled in distilled water.

The sample was prepared for analysis by filtration through a Gooch crucible mounted in a Witt filtering apparatus,[2] essentially a suction flask with a ground glass cover. The Gooch was made with asbestos, washed acid and alkali free, and prepared with distilled water. The filtrate was received in a small clean test tube, the necessity of washing the contents from a large receptacle being thus eliminated. This method is very rapid and gave a clear filtrate.

Determination of p_H by the Colorimetric Method.—The p_H was determined by the colorimetric method essentially as described by one of us (A. T. S.).[3] The indicators used were: brom phenol blue, 0.1 per cent. in 70 per cent. alcohol, p_H 3.0-p_H 4.6; methyl red, 0.1 per cent. in 95 per cent alcohol, p_H 4.6-p_H 6.2; thymol blue, 0.1 per cent. in 70 per cent alcohol, p_H 1.3-p_H 3.0, p_H 8.0- p_H 9.6.

Standard solutions were prepared according to the directions given by Clark and Lubs. To 2 c.c. of a standard solution of known p_H contained in small bottles were added 2 drops of indicator. In similar small bottles, 1 c.c. of filtrate and 1 drop of indicator were mixed and comparison made in a color box. Two indicators only were required, except in very rare instances, brom phenol blue and methyl red. The methyl red standards faded rapidly and had to be made fresh every few days. Standards were made up at intervals of 0.2 p_H. Readings in most cases were clear cut to within 0.1 p_H. Because of the protein, salt and opacity factors, the color produced by the indicators occasionally failed to fit into the standard color series. This difficulty arose chiefly with brom phenol blue at about p_H 4.3. Reading by mercury vapor light and by compensation helped to correct this difficulty. Readings checked by the electrometric method were found to show good agreement to within 0.1 p_H. In a single case, an error of 0.35 p_H was found.

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[2] This may be obtained from Eimer & Amend (No. 2894).

[3] Shohl, A. T., and King, J. H.: Determination of the Acidity of Gastric Contents. I. Determination and Significance of Acidity. II. The Colorimetric Determination of Free Hydrochloric Acid. III. Combined Acidity and Buffer Value, Bull. Johns Hopkins Hospital **31**:152 (May) 1920.

RESULTS

The Normal Range of the Hydrogen-Ion Concentration.—Data are presented on a study of 227 observations on the p_H of gastric contents of forty-three infants from 3 to 19 months old. All of the infants studied in this series were artificially fed. All were in the hospital with the exception of those in Cases 136 to 141; these six were in the Babies' Emergency Home, and were considered normal. Nine additional infants were considered normal, though hospitalized; e. g., with cases of chickenpox in the third week, etc. Accordingly, the determination of the normal range, with so many of the subjects subnormal physically, is open to criticism. It seemed not unreasonable nor illogical to assume, however, that a majority of the cases undergoing treatment for a variety of conditions, had a normal gastric acidity, since acutely ill children were not included in the series, except those with tetany.

In the first ninety determinations on the standard meal, removed at the end of an hour, irrespective of age, amount fed and disease, cases with readings above p_H 5.0 seem to fall into the following groups: (1) tetany cases, early and untreated; (2) a few cases in which an unusually large amount could be removed, i. e., cases with a slow emptying time; (3) cases of severe illness—acute adenitis, cases accompanied by severe vomiting, a case of hydrocephalus following meningitis, etc. Excluding these from the present discussion, the normal range on this particular meal, for all ages, at sixty minutes, varied from p_H 3.2 to p_H 5.0, with a majority of them (76 per cent.) between p_H 3.9 and p_H 4.6.

Davidsohn[4] considers p_H 5.1 as the normal average for nine infants under 4 months on one third milk (variations from 4.1 to 5.8), and for nine infants under 4 months on two thirds milk, p_H 4.9 (with variations from 3.1 to 5.6) as the normal average.

Salge,[5] Huenekens,[6] Kronenberg,[7] Theile[8] and Hess[9] have all found values which roughly correspond with these. We found a slightly higher acidity, as could be expected from a skim-milk test meal. The exact value cannot be profitably discussed until the variable factors have been evaluated.

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4. Davidsohn: Footnote 1, second reference.

5. Salge, B.: Sälzsäure im Säuglingsmagen, Ztschr. f. Kinderh. **4**:171-173, 1912.

6. Huenekens, E. J.: Die Acidität des Mageninhalts im Säugling und Kindesalter bei milch- und fleischhaltiger Probenahrung, Ztschr. f. Kinderh. **11**:297-303, 1914.

7. Kronenberg, R.: Azidität und Pepsinverdauung im Säuglingsmagen, Ztschr. f. Kinderh. **82**:407-422, 1915.

8. Theile, P.: Ueber die Herstellung bestimmter Aciditätswerte im Säuglingsmagen und deren Einfluss auf die Entleerung, Ztschr. f. Kinderh. **15**:318-356, 1917.

9. Hess, R.: Die Azidität des Säuglingsmagens, Ztschr. f. Kinderh. **12**: 409-439, 1915.

Error Involved in Fractional Samples.—White [10] recently showed that the acidity of gastric contents, as estimated from small samples removed for fractional work, might vary considerably. He considered this due to incomplete mixing of acid secretion with the contents of the stomach. He concludes: "Fractional analysis is only a rough method of testing gastric secretion; accidental variation may amount to 50 or 100 per cent. of the figures obtained. Only gross changes in acidity have clinical importance."

To confirm this work, a series of seventeen cases was studied, in which small amounts of the contents were removed within a few seconds of one another. The p_H was determined on a portion of each sample; the various samples were then mixed, and the p_H of the mixed specimen obtained.

Of the seventeen cases, fourteen showed an average variation of 0.4 p_H. Three showed a much greater variation, 1.1, 1.1 and 1.3 p_H; but in all three of these cases, of the six or seven samples removed, all but one were fairly consistent, there being in each case one single determination markedly different from the others. Thus, the readings were in one p_H 5.9, 5.7, 5.8, 5.5, 5.5, 5.2 and 4.8; in another, p_H 5.5, 5.6, 5.7, 5.6, 5.4 and 4.4; and in the third, p_H 4.0, 4.4, 4.4, 4.4, 4.6 and 5.1. These three abnormal figures out of eighty-five consistent values suggest some other explanation than variations in the gastric secretion or mixing; e. g., the tube's having been pushed into the duodenum; regurgitation of intestinal contents or swallowing of saliva. However, an error of 0.4 p_H is great enough to require elimination of small samples, and in subsequent work attempt was made to empty the stomach. This does not apply to the fractional determinations necessary in the study of digestion in relation to time. In that study, the error of the method is recognized.

Davidsohn [4] has also tested the variation in small samples and came to similar conclusions. He found an average error of 0.3 p_H and a variation greater than this in one fourth of the cases.

The Time Factor.—Figure 1 was made by plotting the p_H of samples removed at various times following the ingestion of 100, 150 or 200 c.c. of the standard meal. It is composed of twenty series of readings made on nine infants, without regard to age or disease.

Even though we allow for the error involved in estimating the p_H from single samples rather than from entire contents, the results are remarkably constant. They illustrate graphically the increase in p_H with the increase in digestion time. The p_H can be approximated as 6.0 at twenty minutes; 5.3 at thirty minutes; 5.0 at forty minutes;

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[10] White, F. W.: Simultaneous Variation in Acidity of Different Portions of Gastric Contents, J. A. M. A. **79**:1499-1503 (Oct. 28) 1922.

4.8 at fifty minutes; 4.5 at sixty minutes; 4.3 at seventy minutes; 4.2 at eighty minutes; 4.1 at ninety minutes, and 3.9 at 120 minutes.

The results of this study emphasize the fact that conclusions drawn from work such as this must take into account the time factor. To be comparable, estimations of p_H must be made on contents removed after the same digestive interval.

Davidsohn[4] has shown that, on one third whole milk, for 100 c.c. at one hour, the p_H was 5.1; for 150 c.c. at one and a quarter hours, 5.32; at one and a half hours, 4.88, and at two hours, 4.90. With two thirds whole milk, 200 c.c. in every case, he found the p_H at one and a half hours was 5.30; at one and three-quarter hours, 5.10; at two hours, 5.03, and at two and a quarter hours, 4.70. This shows a definite increase with increasing time. If he had fed smaller amounts and removed the contents sooner, the increase in acidity would have been even greater.

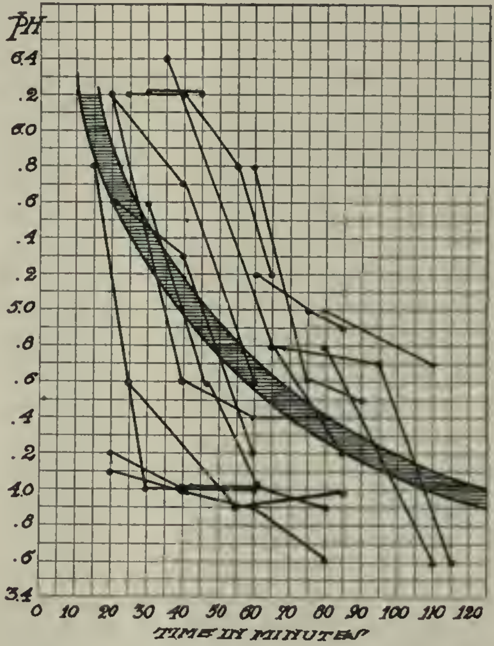

Chart 1.—The increase in acidity of gastric contents with increase in digestive period, without regard to age, condition or amount fed.

No point in these data represents the p_H of the stomach in its resting condition. The exact point at which this was reached could not be determined on the dilute test meal used because of our inability to obtain sufficient amounts for analysis. To obtain an approximation of this figure, lavage of the stomach with 25 c.c. of distilled water four hours after feeding was done. This resulted in the following values: p_H 3.0, 3.3, 3.2, 3.0, 3.6, 3.7 and 3.5. These determinations are open to the criticism that they do not accurately represent the p_H of the gastric secretion of the fasting infant, (1) because of the dilution with so much water; (2) because of the possibility of the presence of a residuum from the feeding four hours before, or (3) because of psychic secretion of gastric juice. They are not considered to represent the actual fasting acidity, but an approximation of the chemical state of the stomach at the starting point, the introduction of the meal.

Relation of Previous Type of Feeding.—The children on whom this study was made were all on a diet which had milk for its basis. The older ones received in addition vegetable puree, broth, farina and orange juice. In no case was meat a constituent of the diet. The oldest child was 19 months, the youngest 2. Some of these were studied over a period when their diet was changed from a sweet to a sour milk mixture and back again.

TABLE 1.—*Relation of p_H to Amount of Test Meal and Age*

100 C.c. Fed		150 C.c. Fed		200 C.c. Fed	
Age, Months	p_H	Age, Months	p_H	Age, Months	p_H
5	3.6	9	4.7	9	4.7
5	3.6	9	4.3	15	5.7
5	4.6	4	5.3	12	4.1
2	4.6	4	5.5	12	4.1
2	4.6	4	5.5	17	4.0
2	4.6	15	3.6	17	4.1
2	4.6	4	4.8	8	4.3
3	4.6	4	4.0	8	5.2
5	4.4	4	4.3	8	4.0
5	4.0	5	4.0	8	5.1
19	4.4	5	4.0	3	4.0
19	4.0	13	4.1	3	5.1
9	4.4	4	4.9	15	5.2
4	5.0	8	4.9	15	4.0
5	3.9	9	4.3	15	4.2
12	3.8	..	...	15	4.0
5	5.4	..	...	15	3.7
3	5.2	..	...	15	4.8
5	3.5	..	...	4	5.5
..	...	..	...	13	5.0
..	...	..	...	13	5.0
..	...	..	...	9	4.0
Aver. 6.2	4.3*	6.6	4.5*	11.3	4.5*

* The average acidity is represented by a numerical average of the p_H values.

We concluded that an alteration in diet which did not involve removal of milk as the basis of the diet did not alter the reaction of the stomach to a test meal.

Influence of Age on p_H.—Table 1 includes fifty-five observations made on gastric contents of thirty-one babies fed on varying amounts of the standard meal. Of these, twenty-two ranged in age from 2 to 9 months; the other nine, from 12 to 19 months.

The average p_H of the younger group, obtained numerically, regardless of the amount fed, was p_H 4.6. The older group showed an average, regardless of the amount fed, of p_H 4.2.

Hence, with increasing age, there is an increase in acid production. Davidsohn [3] was unable to show that age increased the acidity markedly except in the case of breast milk. Kronenberg [7] showed that under 8 months, the values average about p_H 5.0, but in infants from 10 to 21 months, the values were about 4.0.

Effect of Quantity of the Test Meal on p_H.—A study of the amount given (Table 1) shows that the p_H approximates a normal value, which is p_H 4.3-4.5. Since, however, the values for 100 c.c. were mostly on the younger group and for 200 c.c. mostly on the older group, this statement may be misleading, for it involves two factors. In order to determine the effect both of age and of amount fed, the values were separated into six groups, three for the younger infants and three for the older. The values given in Table 2 show that, with larger test meals, there is a diminished acidity, in spite of the fact that the secretion of hydrochloric acid is increased. The members of the older group show a greater acid secretion in every case.

TABLE 2.—*The p_H of Gastric Contents for Different Amounts of Test Meal and Different Ages*

	100 C.c.		150 C.c.		200 C.c.	
	p_H	C.c. N/10	p_H	C.c. N/10	p_H	C.c. N/10
Younger group (5.4 months).......	4.3	60*	4.6	80*	4.7	100*
Older group (14.3 months).........	4.0	75*	3.9	110*	4.6	110*

* The values are estimated from the titration values given in the discussion of the test meal.

TABLE 3.—*Relation of p_H to Concentration of Test Meal*

	p_H	Meal	p_H	Meal	p_H	Meal	p_H
M. W.	3.3*	6/150†	4.9	12/150	5.5	24/150	5.7
E. P.	3.0	......	...	16/200	4.1	32/200	4.9
M. R.	3.2	......	...	16/200	4.7	32/200	6.1
D. A.	3.7	......	...	12/150	4.4	32/200	5.5

* In this column is given a figure obtained when the stomach was lavaged with 25 c.c. of distilled water at a time when the baby would normally have received its regular feeding (i. e., when the stomach was practically empty, four hours after the previous feeding).

† The fraction given under the heading "Meal" was made up as follows: The numerator represents grams of powdered milk; the denominator, cubic centimeters of distilled water.

Thus, the members of the older group secrete more acid for a given amount of test meal and are also able to secrete more acid when larger test meals are given. The result is a more acid gastric content.

Effect of Concentration of Test Meal on p_H.—To study the effect of its concentration on p_H, the composition of the test meal was varied and a study made on four babies on whom we had previously made a number of determinations with the standard meal. The concentrations represent half milk, whole milk, and "double" milk. The results of this study are incorporated in Table 3.

The data show that, with increasing concentration of the test meal, the acidity of the gastric contents will be correspondingly decreased. In the presence of a greater amount of buffer substances to be neutralized by the gastric juice, the stomach is unable to secrete enough acid to bring the contents to the normal p_H.

Relation of p_H to Amount Recovered.—It is not essential for emptying of the stomach to have an acid stomach contents; for Theile[8] has shown that milk made alkaline with phosphates leaves the stomach rapidly. But under physiologic conditions, on a given meal the acidity must play a part. Davidsohn[4] states in a case of a very acid finding, "the contents removed were only 8 c.c."

Figure 2 was constructed by charting against the p_H the average amount recovered at that p_H.

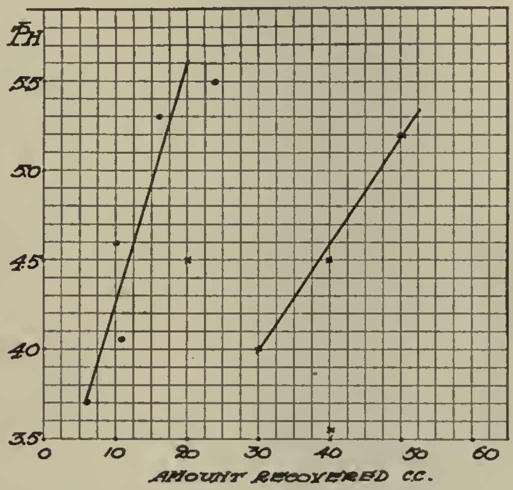

Chart 2.—The relation of acidity to the average amount recovered at that p_H. Dots indicate 100 c.c. fed; crosses, 200 c.c. fed.

The diagram indicates that, with increasing p_H, a larger amount is recovered. Therefore, the more acid the contents, the more rapidly the stomach empties. The steeper slope of the curve for the smaller amount fed indicates that the p_H is more important here than for the larger amounts, in which other factors take part also.

COMMENT

The acidity of the gastric contents in infancy approximates p_H 5.0, as first shown by Allaria[11] and first in this country by Hahn.[12] This acidity is a resultant of a number of factors, some of which have been studied; others are unknown. The factors can be grouped into those due to the food and those of the individual.

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[11] Allaria, G. B.: Untersuchungen über Wasserstoffionen-Koncentrationen im Säuglinsmagen, Ztschr. f. Kinderh. **68**:259-285, 1907.

[12] Hahn, M.: Gastric Digestion in Infants, Am. J. Dis. Child. **7**:305-314, 1914.

The kind of food used determines the amount of acid necessary for digestion. Skimmed cow's milk has a higher buffer value than breast milk; therefore, it requires a greater amount of acid to bring it to a given acidity. Increasing the amount of food or increasing the concentration increases the total buffer substance and therefore increases the acid requirement. The more acid the food is initially, the less acid is required to bring the gastric contents to a given p_H. This reasoning has led Marriott[13] to feeding lactic acid milk. Davidsohn[4] has shown similar effects with protein milk as well as with buttermilk.

The reaction of the stomach to food is complex. At least two factors stand out. First, there is a definite hydrogen-ion concentration, an optimum acidity toward which the organism strives. What the significance of this acidity is and its relation to peptic digestion have been reviewed by Davidsohn.[14] The fact of importance to us is that, when this acidity is attained, gastric secretion ceases. The other factor is the ability of the stomach to increase the acid secreted when more work is given it. The secreting capacity of infants is limited, so that when larger amounts of food or more concentrated foods are given, they are no longer able to reach the optimal acidity. In our series of cases, the amount usually secreted can only be doubled. There is a very small factor of safety.

The factors which govern the emptying of the stomach include the amount of fat, amount of water, consistency of food, gastric motility and tonus and the acidity of the contents. When the acidity is greater, the emptying time is shorter, and the two are interdependent. The influence of age, amount and kind of feeding, concentration and other variables on the p_H of the gastric contents permits a more exact estimate of the values obtained for diagnostic purposes or regulation of the feeding.

SUMMARY AND CONCLUSIONS

1. The normal range of the p_H of the gastric contents on the milk test meal at the end of an hour is p_H 3.2-p_H 5.0, with 76 per cent. of the readings between p_H 3.9 and p_H 4.6.
2. The error of determining acidity of gastric contents from samples rather than entire contents is p_H 0.4.
3. The acidity increases with increase in time.

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[13] Marriott, W. McK.; Davidson, L. T., and Harshman, L. T.: Studies on the Digestion in Infancy. Hydrogen-Ion Concentration of the Gastric Contents, Tr. Am. Pediat. Soc. **34**:39-45, 1922.

[14] Davidsohn: Footnote 1, first reference.

4. The previous type of feeding has no effect on the test meal.

5. Acid production and hydrogen-ion concentration increase with increase of age.

6. A fourfold increase of the concentration of the test meal decreases the hydrogen-ion concentration.

7. A twofold increase of the amount of the test meal causes a stimulation of acid secretion, but a lessened acidity.

8. The greater the gastric acidity, the more rapidly the stomach empties.

GASTRIC ACIDITY IN INFANTILE TETANY*

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In the preliminary physiologic study of the gastric contents of infants,[1] it was noted that those babies who were suffering from tetany presented gastric findings which differed markedly from those of normal infants. Therefore, a special study of eleven cases of manifest tetany was undertaken this past year.

Tetany was diagnosed clinically on the history or presence of an inspiratory crow, carpopedal spasm, convulsions and positive Chvostek and Trousseau signs. The diagnosis was confirmed by the electrical reactions of Erb, but the ultimate criterion for the diagnosis and progress of the disease was the calcium content of the blood. This, as has been shown by Howland and Marriott,[2] and others, may fall in active tetany from the normal values of 10 to 11 mg. per hundred cubic centimeters of serum to as low as 3.5 mg., the average being about 5.5 mg. per hundred cubic centimeters. Symptoms of tetany are present when the serum calcium is below 7.5 mg. per hundred cubic centimeters. The calcium concentration returns toward normal levels coincidently with the relief of clinical symptoms.

The eleven cases of infantile tetany studied are abstracted in the protocol below. All of them showed associated rickets, mainly of the so-called "head rickets type"; craniotabes was present in eight of the cases and enlarged frontal bosses in two of the remaining three cases. Both of the latter were in babies over 11 months old. As has been frequently noted, tetany occurs more often in the spring. Seven of the cases in our series were treated in May, one in April, one in March, one in February and one in January. Six cases gave a definite history of onset of symptoms of tetany coincident with the development of fever, generally caused by an upper respiratory infection. The most common clinical manifestation of tetany was the Chvostek sign, which was present in eight cases. The electrical reactions were those of active tetany in all cases. The serum calcium was low in every case, the average reading of the first analysis being 5.9 mg. per hundred cubic centimeters.

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* From the Department of Pediatrics, Yale University School of Medicine.

[1] Babbott, F. L., Jr.; Johnston, J. A.; Haskins, C. H., and Shohl, A. T.: Hydrogen-Ion Concentration of Gastric Contents in Infants, this issue, p. 475.

[2] Howland, John, and Marriott, W. McK.: Observations Upon the Calcium Content of the Blood in Infantile Tetany and Upon the Effect of Treatment by Calcium, Quart. J. Med. **11**:289-319 (July) 1918.

Test meals were analyzed thirty-eight times at various stages of the disease. The meal consisted of 16 gm. of powdered milk and 200 cubic centimeters of water, a mixture having a p_H of 6.2, and was substituted for the regular formula and given approximately four hours after the last feeding. After one hour, all available gastric contents were removed through a tube with three fenestrations. The amount of gastric contents removed was measured and its p_H determined by the method of Shohl and King.[3] Under these given conditions, the hydrogen-ion concentration of the gastric contents of normal infants of from 4 to 12 months of age varies between p_H 3.9-4.6.[1] In order to cause as little psychic disturbance as possible, the meal was not forced, nor was gavage carried out, except in two instances, in each of which irregular values were obtained. During the period of digestion, the baby was not disturbed by any clinical or laboratory procedure. The amount of ingested food was kept as nearly constant as possible. Infants could not always be made to take the required amount and sometimes vomited part or all of the food taken. The amount fed was measured and the amount of vomitus estimated, so that the percentage returned could be calculated. Six of the infants took all their feedings without vomiting or refusing any food. The use of a dental suction apparatus to remove saliva was considered, but was thought to present too many practical and emotional difficulties to warrant its use. Pyloric regurgitation was recognized to be a source of error, so frequent tests for bile in the gastric contents were made. The few cases which gave a positive reaction were not included in the series. Although proper evaluation of the importance of these difficulties cannot at this time be made, slight changes in the hydrogen-ion concentration of the gastric contents may be regarded as of little significance. Conclusions have only been drawn on a difference of 0.3 of a p_H or more.

Analysis of the findings in these cases during active tetany revealed a definite and marked lowering of the acidity of the gastric contents. All of the values indicated a lower acidity than did those found in normal infants, the average p_H on the first analysis in each of the eleven cases being 5.3. The acidity returned to normal values synchronously with the relief of clinic symptoms of tetany, the average p_H of the final tests being 4.2. There was also a coincident rise of the calcium content of the serum from an average of 5.9 mg. per hundred cubic centimeters at the beginning to an average of 8.8 mg. at the close of the period of observation. The close relationship between the rising gastric acidity and the rising blood calcium during convalescence from manifest tetany is shown graphically in Charts 1 and 2. In some instances, the

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3. Shohl, A. T., and King, J. H.: Determination of the Acidity of Gastric Contents. I. Determination and Significance of Acidity. II. The colorimetric Determination of Free Hydrochloric Acid, Bull. Johns Hopkins Hosp. **31**:152-162 (May) 1920.

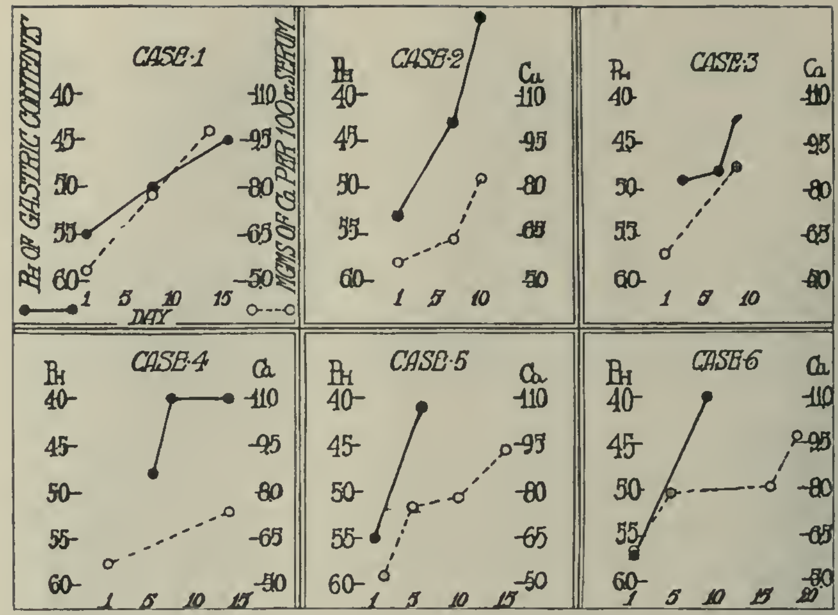

Chart 1.—Findings in Cases 1-6. The solid line in this chart and in Chart 2 represents the acidity of the gastric contents charted against p_H values recorded in the left hand column. The broken line represents the number of milligrams of calcium per hundred cubic centimeters of serum as recorded in the right hand column.

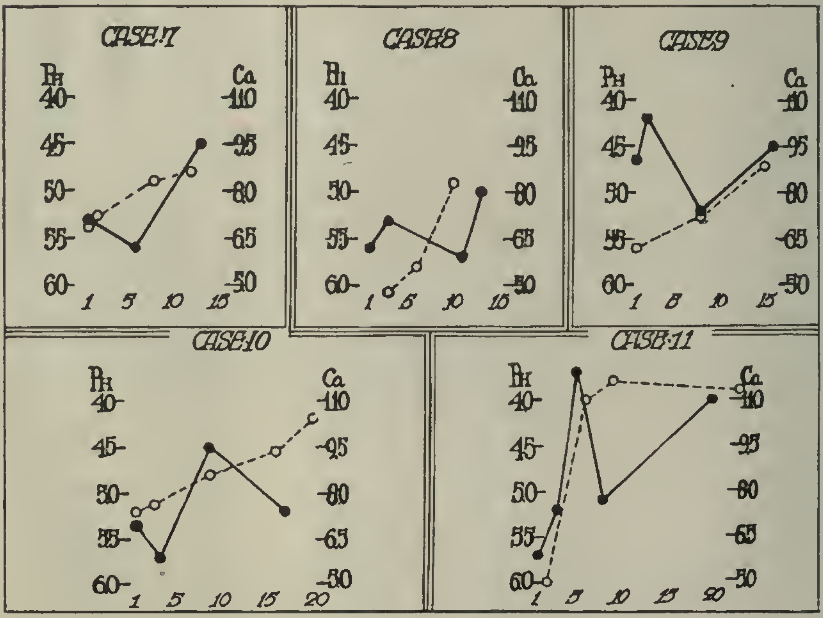

Chart 2.—Findings in Cases 7-11.

gastric acidity does not increase steadily; many of the bizarre findings, however, can be explained by intercurrent infections or by feeding difficulties which are analyzed in the protocol, but the general trend toward normal values is clearly demonstrated.

Delayed emptying time or increased gastric retention was also found to be present in manifest tetany. A greater proportion of the test meal was recovered from these infants than from those that were normal. The average amount ingested for the first test meal was 167 c.c., of which 33 per cent. was recovered. During convalescence from tetany, the gastric motility increased so that, of the last meal, which averaged 180 c.c., only 28 per cent. could be withdrawn. The more rapid emptying of the stomach is closely associated with the increase of the gastric acidity; for in normal infants, as well as in laboratory animals,[4] when there is a high gastric acidity, there is a correspondingly active gastric motility.

Tetany presents itself as a symptom-complex of many diseases and disturbances of metabolism. At the present time, these various disturbances seem unrelated and lacking in common factors. The symptom-complex dealt with in this paper is that recognized as infantile tetany. This type has been characterized by its association with previously disturbed metabolism (rickets), and by a lowered calcium content of the serum. The connection between rickets and tetany has long been recognized and the relationship between the lowered serum calcium and the progress of the disease has been many times observed, but so far as has been determined, no previous studies of associated gastric findings have been made.

Infantile tetany has been simulated in at least two [5] reported cases of adult tetany. Both presented evidence of decreased gastric acidity and of gastric hypotonus, lowered serum calcium and underlying chronic metabolic disease. One occurred in the terminal stages of sprue, and the other followed diarrhea of many months' duration and of unknown etiology. The first case showed no free or combined hydrochloric acid in the vomitus; the blood calcium findings varied between 8 and 6.5 mg. per hundred cubic centimeters of serum, and postmortem examination disclosed a ruptured appendix and a much dilated stomach. The second case had blood calcium readings between 6 and 4.2 mg. of calcium per hundred cubic centimeters of serum. The gastric analysis at one time showed a total acidity of 5 and free hydrochloric acid absent. A second gastric analysis showed a total acidity of 22 and free hydrochloric of 7 c.c. tenth-normal. Roentgen-ray studies of the gastro-intestinal tract at the time of the first gastric analysis revealed marked gastric stasis or delayed emptying time. At this period, the patient was having manifest tetany. A second roentgen-ray series two months later, when the patient was temporarily free from tetanic symptoms, disclosed a normal gastric motility. At that time, no chemical analyses of gastric contents were made.

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[4] Hedblom, C. A., and Cannon, W. B.: Some Conditions Affecting the Discharge of Food from the Stomach, Am. J. M. Sc. **138**:518, 1909.

[5] Barach, A. L., and Murray, H. A., Jr.: Tetany in a Case of Sprue, J. A. M. A. **74**:786-788 (March 20) 1920. Underhill, F. P.; Tileston, W., and Bogert, J.: Metabolism Studies in Tetany, J. Metabolic Research **1**:723-736 (June) 1922.

Diminished gastric acidity and tonus[6] associated with low serum calcium[7] is present in tetany following the removal of parathyroid glands from dogs.

The symptoms of tetany, in the infantile and experimental (parathyroidectomy) types, at least, are asssociated with the lowering of the calcium in the blood. If the calcium can be brought back to normal, the manifestations of the disease disappear. Infantile tetany has been treated by oral administrations of calcium chlorid and of calcium lactate[2] and by intravenous infusions of calcium lactate.[8] The recovery is much hastened if cod liver oil and phosphorus[8] are given for the underlying rickets, at the same time that the calcium is given to control the tetany. Calcium therapy produced varying results in the two cases of adult tetany referred to above. Infusions of calcium lactate failed to raise the blood calcium in the case of tetany complicating sprue; whereas, calcium chlorid and calcium carbonate relieved symptoms of tetany in the patient suffering from protracted diarrhea. Dogs also that have undergone parathyroidectomy can be kept free from tetany symptoms by intravenous administrations of calcium chlorid,[9] or by feeding large doses of calcium lactate[10] or large quantities of milk.[11] Various types of treatment were employed in the cases of this series, but as far as the gastric findings were concerned, no difference in treatment could be detected. Recently, Casparis and Kramer,[12] and also Hoag,[13] have shown that, even though no calcium is administered, tetany can be cured by exposure to radiations of a quartz mercury vapor lamp.

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[6] Keeton, R. W.: The Secretion of the Gastric Juice During Parathyroid Tetany, Am. J. Physiol. **33**:25-49, 1914. Carlson, A. J.: The Tonus and Hunger Contractions of the Empty Stomach During Parathyroid Tetany, Am. J. Physiol. **32**:398-404, 1913. Carlson, A. J.: The Conditions of the Digestive Tract in Parathyroid Tetany in Cats and Dogs, Am. J. Physiol. **30**:309-340, 1912.

[7] Hastings, A. B., and Murray, H. A., Jr.: Observations on Parathyroidectomized Dogs, J. Biol. Chem. **46**:233-256 (March) 1921.

[8] Brown, Alan; McLachlan, I. F., and Simpson, R.: The Effect of Intravenous Injections of Calcium in Tetany and the Influence of Cod Liver Oil and Phosphorus on the Retention of Calcium in the Blood, Am. J. Dis. Child. **19**: 413-428 (June) 1920.

[9] Wilson, D. W.; Stearns, T., and Thurlow, M. DeG.: The Acid-Base Equilibria in the Blood After Parathyroidectomy, J. Biol. Chem. **23**:89-109, 1915. Salvesen, H. A.: Studies on the Physiology of the Parathyroids, Proc. Soc. Exper. Biol. & Med. **22**:204-210, 1923.

[10] Salvesen, H. A.: Footnote 9, second reference. Luckhardt, A. B., and Goldberg, Benjamin: Preservation of the Life of Complete Parathyroidectomized Dogs by Means of the Oral Administration of Calcium Lactate, J. A. M. A. **80**:79-80 (Jan. 13) 1923.

[11] Salvesen, H. A.: Footnote 9, second reference.

Why should there be a diminished calcium content of the blood in infantile tetany? The diets of most infants with tetany contain an adequate amount of calcium. Is the symptom-complex partially a question of faulty calcium assimilation? Is there any connection between the lowered gastric acidity here reported and the assimilation of calcium from the gastro-intestinal tract?

Calcium is known to remain in solution only in an acid medium and presumably may be absorbed only from such a medium. A search of the literature reveals little information regarding calcium absorption. In 1907, Von Noorden [14] says: "The insoluble calcium salts are dissolved in the stomach to a greater or less extent, depending on the amount of hydrochloric acid present. They are only there absorbed, however, in the merest traces, the greatest absorption occurring in the upper parts of the small intestine. There, the dissolved calcium solutions are transformed again into neutral or acid calcium carbonates and phosphates, and into the salts of fatty acids, the amount taken up by the body depending on the reaction of the intestine, and on the quantity of carbonic acid and phosphoric acid, and upon the various fermentation acids present." He states further [14] that "in cases of hypomotility associated with dilatation and stagnation, the gastric absorption, which is normally very slight, is further reduced."

Recently, Steenbock [15] and his co-workers have reported a most interesting study of calcium absorption. They found that many calcium salts, all of which remain soluble only in an acid medium, can be absorbed from the gastro-intestinal tract. Barium salts which are not soluble in an acid medium can be fed in large doses without producing toxic symptoms. From these findings, he says, "It is undoubtedly the acidity which makes possible the assimilation of the difficultly soluble calcium salts from the intestine." The hypothesis of the necessity for an adequate acidity for calcium absorption is borne out by a relatively new treatment for tetany. It has been found that the disease can be cured by adding acid [16] or acid-forming substances [17] to the diet. In this same connection, it is interesting to note that Marriott [18] states that he has never seen a case of tetany develop in a baby fed on lactic acid milk.

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[12] Casparis, H., and Kramer, B.: The Treatment of Active Infantile Tetany with Radiations from the Mercury Vapor Quartz Lamp, Bull. Johns Hopkins Hosp. **34**:219-220, 1923.

[13] Hoag, Lynne: The Treatment of Infantile Tetany with Ultraviolet Radiation: Its Effect on the Clinical Symptoms and on the Calcium Concentration in the Blood Serum, Am. J. Dis. Child. **26**:186-194, (Aug.) 1923.

[14] Von Noorden, K. H.: Metabolism and Practical Medicine, Chicago, W. T. Keener & Co., 1907. p. 38.

[15] Steenbock, H.; Hart, E. B.; Sell, M. T., and Jones, J. H.: The Availability of Calcium Salts, J. Biol. Chem. **56**:375-386, 1923.

The question now arises: Why should a rachitic infant suddenly develop tetany? Most cases of tetany give a definite history of infection with fever at the onset of the manifestations of the disease. It has been shown that fever, both in laboratory animals [19] and in infants,[20] is responsible for a sudden and marked diminution of gastric acidity and of gastric motility.[21]

The following chain of events suggests itself as a possible mechanism of the production of tetany in many cases of infants. A rachitic infant develops an infection with fever, which, in turn, gives a diminished gastric acidity. The gastro-intestinal contents, therefore, afford a less favorable medium for calcium solution and calcium assimilation. This results in a lowering of the calcium content of the blood, which is responsible for symptoms of tetany.

SUMMARY

Lowered gastric acidity and diminished gastric emptying time are found in manifest infantile tetany. There is a return of the gastric content to normal acidity and of the gastric motility to normal activity, coincident with the rise of serum calcium to normal, and with the disappearance of clinical symptoms of tetany.

Cases 1, 5, 6, 7, 9 and 10 were seen at the Infants' Hospital, Boston. Calcium determinations in these cases were made by the Kramer and

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[16] Wilson, D. W.; Stearns, T., and Janney, J. H., Jr.: The Effect of Acid Administration on Parathyroid Tetany, J. Biol. Chem. **21**:169-177, 1915. Gamble, J. H., and Ross, G. S.: The Effect of Ingestion of Hydrochloric Acid Producing Substances on the Acid-Base Metabolism of an Infant and the Probable Manner of Their Action in the Treatment of Tetany, Am. J. Dis. Child. **25**: 470-497 (June) 1923.

[17] Gamble and Ross: Footnote 16, second reference.

[18] Marriott, W. McK., personal communication to the authors.

[19] Meyer, J.: Cohen, S. J., and Carlson, A. J.: Gastric Secretion During Fever, Arch. Int. Med. **21**:354-365 (March) 1918.

[20] Marriott, W. McK.; Davidson, L. T., and Harshman, L. P.: Studies on the Digestion in Infancy. Hydrogen-Ion Concentration of the Gastric Contents, Tr. Am. Pediat. Soc. **34**:39-45, 1922. Davidsohn, H.: Beitrag zur Physiologie und Pathologie der Magenverdauung beim Säugling, Arch. f. Kinderh. **69**:239-255 (April) 1921. Babbott et al.: Foonote 1.

[21] Whether or not there is a slightly diminished gastric acidity in rickets before the onset of tetany is now being investigated.

Tisdall method.[22] Phosphorus was determined by the Bell and Doisy method.[23]

Cases 2, 3, 4, 8 and 11 were seen at the New Haven Hospital. Calcium determinations were made by the Kramer and Tisdall method.[22] Phosphorus was determined by the Briggs Method.[24]

REPORT OF CASES

CASE 1.—*History.*—D. A., aged 5 months, was a normal infant, breast fed for 3½ months, and weaned satisfactorily to a whole milk modification. Orange juice had been given since weaning, but no cod liver oil, and there had been no deliberate exposure to sunlight. Six weeks before, the baby had fever and an inspiratory crow, but no convulsions. The condition has become progressively worse.

Examination.—Rickets; marked craniotabes; enlarged epiphyses at wrists and ankles; a positive Chvostek sign, and suggestive Trousseau sign were revealed.

Treatment.—Feeding of a whole milk modification was continued. Exposure to a quartz mercury vapor lamp was prescribed.

May 11, when the p_H of the gastric contents was 5.0, the baby had temperature of 102 F. This hyperpyrexia may have influenced the gastric acidity. The clinical symptoms of tetany had disappeared by that day.

May 19, feeding was interrupted for ten minutes. The "digestion period" of sixty minutes is estimated from the mean feeding time.

CASE 2.—*History.*—R. A., aged 11 months, a normal infant, breast fed entirely for nine months, and given tastes of table food for the past two months, had had no cod liver oil, and there had been no deliberate exposure to sunlight. Three and one-half weeks before admission, the infant had a "cold" and on the following day had several clonic convulsions. Six days before admission, there was another cold and more convulsions. There had been an occasional "crow."

Examination.—Otitis media; impetigo; rickets, slight beading of ribs and enlargement of epiphyses of wrists; Chvostek and Trousseau signs and crow were revealed.

Treatment.—April 5: Skimmed lactic acid milk was given.

April 6-12: Whole milk modification, with addition of hydrochloric acid, and farina were given.

April 13: Whole sweet milk modification was fed.

Cod liver oil, 12 c.c., was given April 5. None was given thereafter until April 11, when 4 c.c., three times a day, was given. This was continued until April 19. From April 6 until April 12, inclusive, hydrochloric acid was added to the milk given. Sunlight therapy was employed from April 6 to April 19. Calcium chlorid, 15 grains three times a day, was given, April 13-19.

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[22] Kramer, Benjamin, and Tisdall, F. F.: A Clinical Method for the Quantitative Determination of Calcium and Magnesium in Small Amounts of Serum or Plasma, Bull. Johns Hopkins Hosp. **32**:44-48 (Feb.) 1921.

[23] Bell, R. D., and Doisy, E. A.: Rapid Colorimetric Methods for the Determination of Phosphorus in Urine and Blood, J. Biol. Chem. **44**:55-67 (Oct.) 1920.

[24] Briggs, A. P.: A Modification of the Bell-Doisy Phosphate Method, J. Biol. Chem. **53**:13-16 (July) 1922.

TABLE 1.—*Findings in Case 1*

Date	Temperature	Clinical Findings	Chvostek Sign	Other Signs of Tetany	C. C.	A. C.	A. O.	C. O. C. C. T.	Serum Ca	Serum P	G. C. p_H	Feeding Time, Min.	Digestive Period, Min.	Amount Refused, C.c.	Amount Vomited, C.c.	Amount Fed, C c.	Amount Returned, C.c.	Percentage Returned
5/ 4	99	....	Pos.	Crow	0.75	3.0	1.5	2.4	5.39	6.45*	...	..	..	...	...	...	..	..
5/ 5	99	....	Pos.	Crow	...	...	...	...	....	....	5.5	20	75	0	0	200	30	15
5/ 6	99	....	Pos.	Crow	0.5	3.75	0.5	4.0	....	....	...	..	..	...	...	...	..	..
5/ 7	99	....	Pos.	Crow	...	...	...	...	....	....	...	..	..	...	...	...	..	..
5/ 8	99	....	Pos.	Crow	1.0	4.0	1.5	5.0	....	....	...	..	..	...	...	...	..	..
5/10	99 101	No cause for temperature found	.....	.....	...	..	...	...	....	....	...	..	..	...	...	...	..	..
5/11	102	No cause for temperature found	Neg.	Neg.	0.25	4.0	1.5	6.0	7.75	10.32* 8.1	5.0	30	60	0	0	200	50	25
5/14	102	No cause for temperature found	Neg.	Neg.	...	...	...	...	....	....	...	..	..	...	...	...	..	..
5/16	105	Broncho-pneumonia	.....	.....	...	...	...	....	....	....	...	..	..	...	...	...	..	..
5/17	101	Healing	Neg.	Neg.	3.5	7.0	7.5	7.5	9.86	6.24	...	..	..	...	...	...	..	..
5/19	99.5	....	.....	.....	...	...	...	...	....	....	4.5	10, 15	60	0	0	200	50	25

* Phosphorus determined on whole blood.

TABLE 2.—*Findings in Case 2*

Date	Temperature	Clinical Findings	Chvostek Sign	Other Signs of Tetany	C. C.	A. C.	A. O.	C. O. C. C. T.	Serum Ca	Serum P	G. C. p_H	Feeding Time, Min.	Digestive Period, Min.	Amount Refused, C.c.	Amount Vomited, C.c.	Amount Fed, C.c.	Amount Returned, C.c.	Percentage Returned
4/ 5	98	Otitis media paracentesis	Pos.	Trous.	0.75	2.0	1.0	5.0	....	....	...	..	..	...	...	...	..	..
4/ 6	99	....	Pos.	Trous. C-P. spasm	0.5	2.0	1.0	2.0	5.6	3.8	5.3	10	60	0	0	200	?	?
4/ 7	99	....	Pos.	Trous. C-P. spasm	0.5	0.75	0.5	3.0	...	...	...	..	..	...	...	...	..	..
4/ 8	99	....	.....	Trous. C-P. spasm	0.75	2.0	1.0	3.0	...	...	...	..	..	...	...	...	..	..
4/ 9	99	....	.....	.....	1.0	4.0	2.0	4.0	...	...	...	..	..	...	...	...	..	..
4/10	99	....	.....	.....	0.5	2.0	1.5	4.5	...	...	...	..	..	...	...	...	..	..
4/11	99	....	.....	.....	1.25	2.0	1.0	2.75	...	...	...	..	..	...	...	...	..	..
4/12*	99	....	.....	.....	0.75	1.7	1.0	2.5	6.4	...	4.3	.	70	...	...	200	40	20
4/13	99	....	.....	.....	...	...	...	5.0	...	...	...	..	..	...	...	...	..	..
4/15	99	....	.....	.....	...	...	...	5.0	8.3	...	3.2	5	60	0	0	200	52	26
4/16	99	....	Neg.	Neg.	...	...	...	...	...	...	...	..	..	...	...	...	..	..

* Gavage.

CASE 3.—*History.*—R. M., aged 17 months, a normal infant, never breast fed, on a malted milk diet for first eight months and a mixed diet since then, had had no cod liver oil. There had been no deliberate exposure to sunlight. The baby had had occasional colds. One week before admission, severe clonic convulsions and carpopedal spasm developed, with crow and convulsions the day before admission.

Examination.—Bilateral otitis media, tonsillitis and rickets (marked bulging of the forehead, though not true enlargement of the frontal bosses, and very slight enlargement of costochondral junctions) were found.

Treatment.—Whole milk modification with hydrochloric acid was prescribed.

CASE 4.—*History.*—D. A., aged 4 months, a normal infant, breast fed for two months, and given modified cow's milk for the past two months, was given no cod liver oil, and there had been no deliberate exposure to sunlight. For six weeks, there had been loose stools, associated with occasional fever.

Examination.—Otitis media, pharyngitis, rickets (marked craniotabes and enlargement of the anterior and posterior bosses, pallor, slight beading of ribs and enlargement of epiphyses of wrists and ankles), and laryngeal crow were present.

Treatment.—Whole lactic acid milk modification was prescribed, and exposure to quartz mercury vapor lamp.

CASE 5.—*History.*—A. R., colored, aged 6 months, gave a definite history of syphilis, and was possibly premature. The birth weight was 5 pounds (2,268 gm.). The baby had been breast-fed for three weeks, and modified whole milk had been given since then. There had been no digestive disturbance. No cod liver oil had been given and there had been no deliberate exposure to sunlight. The baby did not sit up. Pertussis had been present at 3 months. For two months previous to admission, the patient had had frequent convulsions and inspiratory crow, but was not known to have had fever. There was thought to be loss of weight.

Examination.—The child was very irritable. Rickets (marked craniotabes, enlargement of costochondral junctions and epiphyses of wrists and ankles; positive Chvostek and Trousseau signs, and inspiratory crow were noted.

Treatment.—A whole milk modification was given, and exposure to the quartz mercury vapor lamp was prescribed.

CASE 6.—*History.*—C. R., aged 13 months, a normal infant, breast fed to date, with supplementary feedings of table food for the past seven months, had had no cod liver oil, nor had there been deliberate exposure to sunlight. The baby could not stand alone. Two months previously, it had fever, difficulty in breathing, cyanosis and crow. At this time, twenty-two convulsions occurred in one day. The baby recovered partially, but still crowed and had an occasional convulsion.

Examination.—Rickets (craniotabes, enlargement of costochondral junctions and epiphyses of wrists and ankles), positive Chvostek sign and crow were noted.

Treatment.—A whole milk modification was given, and exposure to the quartz mercury vapor lamp was prescribed.

May 12: The baby had a convulsion while the stomach tube was being passed. No gastric contents were obtained.

May 19: As the baby became cyanotic while the tube was in situ, it was immediately withdrawn, so the total amount of the gastric contents was not determined.

CASE 7.—*History.*—U. W., aged 12 months, a normal infant, never breast fed, had been brought up in a boarding home on proprietary feedings. No cod liver oil had been given and there had been no deliberate exposure to sunlight. The child was not growing, and its history was very unsatisfactory.

Table 3.—*Findings in Case 3*

Date	Temperature	Clinical Findings	Chvostek Sign	Other Signs of Tetany	C. C.	A. C.	A. O.	C. O. C. C. T.	Serum Ca	Serum P	G. C. p_H	Feeding Time, Min.	Digestive Period, Min.	Amount Refused, C.c.	Amount Vomited, C.c.	Amount Fed, C.c.	Amount Returned, C.c.	Percentage Returned
3/ 6	100	....	Pos.	.....	...	...	...	...	5.9	3.93	...	..	..	...	...	...	..	..
3/ 7	100.5	....	Pos.	.....	1.75	4.5	1.5	3.5	....	....	...	..	..	...	...	...	..	..
3/ 8	100	....	Pos.	.....	...	...	...	...	....	....	4.9	10	60	0	0	200	106	53
3/12	99	....	.....	.....	4.0	5.0	5.0+	5.0+	....	....	4.8	15	60	0	50 ? *	200	48	50 (32 ?)
3/14	99	....	Neg.	.....	...	...	...	...	8.75	4.87	4.8	?	60	0	0	200	92	46
4/ 3	...	....	.....	.....	...	...	...	...	....	....	3.9	15	60	0	0	200	100	50

* Vomiting occurred when the tube was being passed.

Table 4.—*Findings in Case 4*

Date	Temperature	Clinical Findings	Chvostek Sign	Other Signs of Tetany	C. C.	A. O.	A. O.	C. O. C. O. T.	Serum Ca	Serum P	G. C. p_H	Feeding Time, Min.	Digestive Period, Min.	Amount Refused, C.c.	Amount Vomited, C.c.	Amount Fed, C.c.	Amount Returned, C.c.	Percentage Returned
2/ 7	100	Otitis media	Neg.	Trous.; erow	0.25	1.0	0.5	1.5	5.7	5.5	...	..	..	...	...	...	..	..
2/10	99	Healed	.....	.....	0.25	1.0	0.5	0.75	...	...	...	..	..	...	...	...	..	..
2/12	99	During morning temperature rose to 101	.....	.....	...	...	...	...	...	...	4.8	20	60	0	45	150	38	25
2/13	101	Paracentesis	.....	.....	...	...	...	...	...	...	...	..	..	...	...	...	..	..
2/14	99	....	.....	.....	0 25	1.0	0.75	1.75	...	...	4.0	10	65	15	15	135	20	14
2/20	99	....	.....	.... .	...	...	...	...	7.3	6.6	4.0	20	70	0	0	150	14	9
2/21	99	....	.....	.....	2.5	1.75	1.25	5.0+	...	...	...	..	..	...	...	...	..	..

Table 5.—*Findings in Case 5*

Date	Temperature	Clinical Findings	Chvostek Sign	Other Signs of Tetany	C. C.	A. O.	A. O.	C. O. C. O. T.	Serum Ca	Serum P	G. C. p_H	Feeding Time, Min.	Digestive Period, Min.	Amount Refused, C.c.	Amount Vomited, C.c.	Amount Fed, C.c.	Amount Returned, C.c.	Percentage Returned
5/14	99	....	Pos.	Trous.; erow	0.25	2.5	1.75	3.5	...	6.27	5.5	8	60	60	0	140	60	42
5/15	99	....	Pos.	Trous.; erow	0.25	2.0	1.5	6.0	5.2	0	.	..	..	...	...	...	..	..
5/18	99	....	Neg.	Neg.	1.5	4.2	2.5	7.0	7.5	0	...	..	..	...	...	...	..	..
5/19*	99	....	.....	Neg.	...	...	...	...	...	....	4.1	30	60	100	0	100	50	50
5/23	99	....	.....	.....	2.0	4.5	4.0	7.0+	7.8	6.61	...	..	..	...	...	...	..	..
5/28	99	....	.....	.....	1.5	2.5	2.5	7.0+	9.3	0	...	..	..	...	...	...	..	..

* A high degree of acidity would be expected. The amount taken was very small and the feeding time long.

TABLE 6.—*Findings in Case 6*

Date	Temperature	Clinical Findings	Chvostek Sign	Other Signs of Tetany	C. C.	A. C.	A. O.	C. O. C. O. T.	Serum Ca	Serum P	G. C. p_H	Feeding Time, Min.	Digestive Period, Min.	Amount Refused, C.c.	Amount Vomited, C.c.	Amount Fed, C.c.	Amount Returned, C.c.	Percentage Returned
5/10	99	....	Pos.	Crow	0.25	2.5	1.0	3.0	5.95	8.10 5.78*	5.3	10	60	50	0	150	85	56
5/11	100	....	Pos.	Crow	0.25	2.5	1.0	2.75	....	....	...	..	..	...	...	...	..	..
5/12	102	Otitis media	.....	.....	...	...	...	...	....	....	...	..	..	...	...	...	..	..
5/14	99	Healed	Pos.	Crow	...	...	...	...	7.94	....	...	..	..	...	...	...	..	..
5/18	99	....	Neg.	Neg.	1.5	5.0	3.0	7.0+	6.6 ?	6.41	4.0	15	65	0	0	200	20	10
5/25	100	....	Neg.	Neg.	1.5	4.0	3.0	7.0+	8.1	8.3	...	..	..	...	...	...	..	..

* Phosphorus determined on whole blood.

TABLE 7.—*Findings in Case 7*

Date	Temperature	Clinical Findings	Chvostek Sign	Other Signs of Tetany	C. C.	A. C.	A. O.	C. O. C. O. T.	Serum Ca	Serum P	G. C. p_H	Feeding Time, Min.	Digestive Period, Min.	Amount Refused, C.c.	Amount Vomited, C.c.	Amount Fed, C.c.	Amount Returned, C.c.	Percentage Returned
5/ 7	99	....	Neg.	.....	2.0	2.75	2.5	7.5	6.9	....	5.3	..	60	0	0	200	30	15
5/ 8	100	....	.....	.....	1.5	3.0	2.5	8.0	7.27	2.13*	...	..	..	...	...	...	..	..
5/ 9	102½	Otitis media	.....	.....	1.5	6.5	3.5	7.5	....	....	...	..	..	...	...	...	..	..
5/11	104	Otitis media; pneumonia	.....	.....	...	...	...	...	....	....	...	..	..	...	...	...	..	..
5/12	101	....	.....	.....	...	...	...	...	....	....	5.6	10	85	0	0	200	52	26
5/14	100	....	.....	.....	...	...	...	...	8.32	2.72	...	..	..	...	...	...	..	..
5/18	102	....	.....	.....	1.0	3.5	3.5	7.0+	8.64	5.7	...	..	..	...	...	...	..	..
5/19	100	....	.....	.....	...	...	...	...	....	....	4.5	15	60	0	0	200	95	47

* Phosphorus determined on whole blood.

TABLE 8.—*Findings in Case 8*

Date	Temperature	Clinical Findings	Chvostek Sign	Other Signs of Tetany	C. C.	A. C.	A. O.	C. O. C. C. T.	Serum Ca	Serum P	G. C. p_H	Feeding Time, Min.	Digestive Period, Min.	Amount Refused, C.c.	Amount Vomited, C.c.	Amount Fed, C.c.	Amount Returned, C.c.	Percentage Returned
5/ 5	102½	Pharyngitis	Pos.	.....	...	...	...	...	...	...	...	..	..	...	...	...	..	..
5/ 6	103½	Pharyngitis	Pos.	.....	...	...	...	...	...	...	5.6	..	..	...	...	...	..	..
5/ 8*	99	Pharyngitis	Pos.	.....	...	...	...	...	4.8	3.6	5.3	..	60	180	0	200	40	22
5/ 9	99	Healed	Pos.	.....	1.0	3.5	3.0	3.3	...	...	...	..	..	...	...	...	..	..
5/11	99	....	Pos.	.....	...	...	...	...	5.6	4.2	...	..	..	...	...	...	..	..
5/15	99	....	Neg.	.....	3.0	5.0+	5.0+	5.0+	8.3	4.0	...	..	..	...	...	...	..	..
5/16†	99	....	Neg.	.....	...	...	...	...	...	...	5.7	5	60	80	0	200	85	43
5/18	99	....	Neg.	.....	...	...	...	...	...	...	5.0	10	65	0	30	200	35	17

* Gavage of 180 c.c. † Gavage of 80 c.c.

TABLE 9.—*Findings in Case 9*

Date	Temperature	Clinical Findings	Chvostek Sign	Other Signs of Tetany	C. C.	A. O.	A. O.	C. O. C. O. T.	Serum Ca	Serum P	G. C. p_H	Feeding Time, Min.	Digestive Period, Min.	Amount Refused, C.c.	Amount Vomited, C.c.	Amount Fed, C.c.	Amount Returned, C.c.	Percentage Returned
5/ 3	101	Otitis media	Neg.	.....	...	...	...	...	....	....	...	..	..	...	...	...	..	..
5/ 4	101	Otitis media	.....	.....	...	...	...	...	6.23	3.42+	4.7	10	70	0	0	200	9	5
5/ 5	99	....	.....	.....	0.75	3.0	1.5	5.0	....	....	4.2	..	..	...	...	200	16	8
5/ 6	99	Healed	.....	.....	0.75	3.0	0.75	5.5	....	....	...	..	..	...	...	...	..	..
5/ 8	99	....	.....	.....	2.0	4.5	2.5	7.5	....	....	...	..	..	...	...	...	..	..
5/10	99	Paracentesis	.....	.....	...	...	...	...	....	....	...	..	..	...	...	...	..	..
5/11	99	....	.....	.....	1.5	4.5	2.5	7.0	7.37	6.3 4.3+	5.2	5	60	0	0	200	10	5
5/16	99	Healed	.....	.....	...	...	...	...	....	....	...	..	..	...	...	...	..	..
5/18	99	....	.....	.....	2.0	4.0	3.5	7.0	8.83	5.98	...	..	..	...	...	...	..	..
5/19	99	....	.....	.....	...	...	...	...	....	....	4.5	5	60	0	0	200	60	30

Examination.—The baby was undernourished and underdeveloped. Rickets (craniotabes and a fontanel admitting the tips of two fingers, enlarged costochondral junctions and epiphyses at wrists and ankles) but no clinical sign of tetany was noted.

Treatment.—May 7-17, a whole milk modification was given, and May 18, whole lactic acid milk. Exposure to quartz mercury vapor lamp was prescribed.

The alkaline reading, May 12, may possibly be explained by the infant's recent fever.

Case 8.—*History.*—D. S., aged 9 months, breast fed entirely for eight months, with farina added to the diet one month previously, had had no cod liver oil or deliberate exposure to sunlight. Four days before admission, he had fever and "pulled at his ears." The next day, he had an inspiratory crow.

Examination.—Pharyngitis; mild otitis media; rickets (marked craniotabes, moderate enlargement of costochondral junctions, marked epiphyseal enlargement at wrists and ankles); positive Chvostek sign; carpopedal spasm, and inspiratory crow were noted.

Treatment.—May 5, whole milk and dextrimaltose were given; May 6 and 7, whole milk, 600 c.c., with hydrochloric acid, tenth normal, 225 c.c. (five feedings). May 8, whole milk mixture, with dextrimaltose, farina, broth and puree, was given. Cod liver oil, 8 c.c. daily, was prescribed, and calcium chlorid, up to 90 grains (6 gm.) a day, May 7-17.

The alkaline reading, May 8, may be explained because of the associated fever. The effect of gavage in the psychic secretions may influence results.

Case 9.—*History.*—S. P., aged 9 months, was a twin, breast fed for five months and weaned to a whole milk modification. At 7 months, farina was added. No cod liver oil was given, and there was no deliberate exposure to sunlight. Three days before, the baby had fever, cough, dyspnea, cyanosis and twitchings of extremities.

Examination.—Otitis media; pharyngitis; rickets (craniotabes, enlargement of the costochondral junctions, enlargement of the epiphyses at the wrists and ankles), but no clinical signs of tetany were noted.

Treatment.—A whole milk modification was given, and exposure to a quartz mercury vapor lamp was prescribed.

The very acid findings of the first two analyses fit in with the small percentage returned, but why there should have been so rapid a gastric emptying time cannot be satisfactorily explained.

May 12, the tube became plugged with mucus and the stomach could not be completely emptied.

Case 10.—*History.*—S. S., aged 5 months, a twin, three weeks premature, whose birth weight was 4 pounds and 5 ounces (1,956 gm.) and who was never breast fed, had gained slowly on whole milk modification, but for past three weeks had vomited. No cod liver oil had been given, and there had been slight exposure to sunlight for the past two weeks. The feeding was regulated because of vomiting. There had been no fever and no convulsions, but the baby had had a "peculiar cry" for the past few weeks.

Examination.—Otitis media; rickets (marked craniotabes, moderate enlargement of costochondral junctions); positive Chvostek and Trousseau signs, and an inspiratory crow were noted.

Treatment.—A whole milk modification was given, and exposure to the quartz mercury vapor lamp was prescribed.

The findings, May 11, as shown in Table 10, when the baby had a temperature of 102 F., cannot be explained at all. The percentage return was very great, and its acidity high. The low acid reading for the last gastric analysis may possibly be explained by the fact that the child was recovering from bronchopneumonia.

TABLE 10.—*Findings in Case 10*

Date	Temperature	Clinical Findings	Chvostek Sign	Other Signs of Tetany	C. C.	A. C.	A. O.	C. O. C. C. T.	Serum Ca	Serum P	G. C. p_H	Feeding Time, Min.	Digestive Period, Min.	Amount Refused, C.c.	Amount Vomited, C.c.	Amount Fed, C c.	Amount Returned, C.c.	Percentage Returned
5/ 3	99	Otitis media	Pos.	Trous.; crow	...	...	...	...	7.4	5.6+	5.5	20	65	45	0	155	40	26
5/ 4	99	....	Pos.	Trous.; crow	1.5	3.5	2.0	5.0	...	...	...	..	..	...	...	...	..	..
5/ 5	99	....	Pos.	Trous.; crow	...	...	...	...	7.6	7.5	5.7	10	65	0	0	200	26	13
5/ 6	99½	....	Pos.	Neg.; crow	1.0	5.0	2.5	7.5	...	...	...	..	..	...	...	...	..	..
5/ 8	100	....	Neg.	Neg.; Neg.	1.5	3.5	2.0	7.5	...	...	...	..	..	...	...	...	..	..
5/10	103	Otitis media; paracentesis	.....	.....	...	...	...	...	...	...	...	..	..	...	...	...	..	..
5/11	102	....	Neg.	Neg.	2.0	5.5	7.5	7.5	8.6	5.3	4.5	25	65	0	0	200	102	51
5/17	102	Pneumonia	.....	.....	...	...	...	...	...	5.1+	...	..	..	...	...	...	..	..
5/18	101	Pneumonia	.....	.....	1.0	5.5	7.0+	7.0+	9.4	6.7	...	..	..	...	...	...	..	..
5/19	101	Pneumonia	.....	.....	...	...	...	...	...	...	5.2	20	60	45	0	155	30	19
5/22	99	Healed	.....	.....	...	...	...	...	10.5	...	...	..	..	...	...	...	..	..

TABLE 11.—*Findings in Case 11*

Date	Temperature	Clinical Findings	Chvostek Sign	Other Signs of Tetany	C. C.	A. C.	A. O.	C. O. C. O. T.	Serum Ca	Serum P	G. C. p_H	Feeding Time, Min	Digestive Period, Min.	Amount Refused, C.c.	Amount Vomited, C.c.	Amount Fed, C c.	Amount Returned, C.c.	Percentage Returned
1/13	100	....	Pos.	.....	1.0	1.5	3.0	1.25	....	...	...	..	..	...	...	...	..	..
1/14	100	....	.....	.....	...	...	...	...	....	...	...	..	..	...	...	...	..	..
1/15*	100-102	....	.....	.....	...	...	...	...	....	...	5.7	20	70	80	80	200	103	51
1/16	103	Otitis media	.....	.....	0.25	3.0	1.25	2.0	5.0	5.6	...	..	..	...	...	...	..	..
1/17	101	Paracentesis	Pos.	.....	...	...	...	...	....	...	5.2	12	60	65	0	200	55	27
1/18	101	....	.....	.....	...	...	...	...	....	...	...	..	..	...	...	...	..	..
1/19	99	....	.....	.....	...	...	...	...	....	...	3.7	15	60	0	0	200	?	?
1/20	99	....	.....	.....	2.0	5.0+	2.5	5.0+	11.0	7.6	...	..	..	...	...	...	..	..
1/21	99	....	.....	.....	...	...	...	...	....	...	...	..	..	...	...	...	..	..
1/22	99	....	.....	.....	...	...	...	...	....	...	5.1	12	60	0	0	200	63	31
1/23	102	Otitis media	.....	.....	1.0	5.0	3.0	5.0+	11.6	6.8	...	..	..	...	...	...	..	..
1/24	100½	Paracentesis	.....	.....	1.5	5.0+	4.0	5.0+	....	...	...	..	..	...	...	...	..	..
1/25	102½	Paracentesis	Neg.	.....	...	...	...	...	....	...	...	..	..	...	...	...	..	..
2/ 3†	99	....	.....	.....	...	...	...	...	....	...	4.0	20	60	160	0	200	62	31
2/ 6	99	....	.....	.....	...	...	...	5.0	11.3	...	...	..	..	...	...	...	..	..

* Gavage of 80 c.c. † Gavage of 160 c.c.

CASE 11.—*History.*—M. C., aged 11 months, had a normal birth, was breast fed up to the present, and had been given tastes of table food for six months. No cod liver oil was given, and there had been no deliberate exposure to sunlight. A crow had been present for ten days.

Examination.—Rickets (anterior fontanel admitting two finger tips, no craniotabes, moderate costochondral and epiphyseal enlargement); enlargement of the spleen, and marked Chvostek sign were noted.

Treatment.—A whole milk modification, puree and farina were given. Calcium chlorid, November 21-January 11, cod liver oil and exposure to the quartz mercury vapor lamp were prescribed.

BOOK REVIEW

LES SYNDROMES ENDOCRINIENS DANS L'ENFANCE ET LA JEUNESSE. By J. Nobécourt, Paris, E. Flammarion, 1923.

This book deals with the endocrine syndromes, particularly during the period of growth. The author cites Hutinel's statement to the effect that the problem of the endocrine glands is not yet crystallized and that caution is necessary in walking such dangerous paths. He certainly tries to exercise this caution, and on the whole with success, making the book very readable.

In the chapter devoted to the thyroid syndromes, the American literature and particularly the contributions from the Mayo Clinic might be utilized to advantage. At any rate, mention of thyroxin should not be omitted. It is somewhat surprising to find as an example of the "forme fruste" of exophthalmic goiter a case presenting a basal metabolic rate 18 per cent. below normal. It is true one hears, even reads, now and then, of a disease combining the features of exophthalmic goiter with those of myxedema. But this is one of the occasions when the greatest caution is necessary and when the data on which such a diagnosis rests has to be given very fully. At least the problematic nature of such an apparently paradoxical syndrome should be pointed out.

That the results of parthyroid therapy in spasmophilia are very doubtful is pointed out. But mention of cod liver oil-phosphorus medication is omitted, and the low calcium content of the blood is not mentioned. The inhibiting result of hypophysis medication on the polyuria of diabetes insipidus is rather boldly attributed to an influence on the renal vessels. The hypophysis syndromes are treated with great reserve. Some of our endocrinologists might read these chapters with much profit. The author justly doubts the existence of any thymic syndromes.

In the chapters on the influence of the sexual glands, the creatin excretion of the eunuch is overlooked. It is recognized that not every form of obesity can be laid to a uniglandular or a pluriglandular syndrome. The relationship of internal secretion to diabetes mellitus is not regarded as sufficiently established for inclusion of this disease in the book. Short discussions of the indications of glandular treatment are given, and here also there is room for improvement.

BOOKS RECEIVED

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THE CAUSATION OF INTRACRANIAL HEMORRHAGES IN THE NEW-BORN *

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An understanding of the causation of intracranial birth hemorrhages, while admittedly important for diagnosis and treatment, is essential for the far more urgent problem of their prevention. Under prevailing conditions, the task of diagnosis and treatment in the main rests with pediatrician and surgeon. The question of prophylaxis, for evident reasons, concerns most of all the obstetrician.

This relative difference of interest in the problem of intracranial birth trauma on the part of the obstetrician, on the one hand, and the pediatrician on the other, finds its expression in the extensive literature of the past decade on this subject. Obstetricians, naturally, have the better opportunity of observing and studying the immediate and especially the mechanical causes of such injuries. They apparently have succeeded in revealing the exact mechanism in the origin of most of the more common types of cranial and intracranial lesions sustained by the child in the course of birth. Pediatricians, who with the rarest exceptions see these patients only later, have made valuable contributions, chiefly in regard to symptomatology. They have discovered the evident etiologic relation of intracephalic birth hemorrhages to a reduced coagulability of the blood, rather frequently ascertainable in the new-born. But, in my belief, pediatricians and surgeons at present greatly overrate the rôle played by hemorrhagic diathesis in the etiology of these hemorrhages. There is danger, I fear, that a wider acceptance of this idea might impair the efforts of obstetricians in regard to the prevention of these lesions.

It is the purpose of this paper to present from the standpoint of the obstetrician the question of the causation of all types of intracranial birth injuries, which, it must be remembered, are not necessarily hemorrhages.

On a previous occasion [1] I had an opportunity to describe in detail a certain confusion of ideas in literature concerning the actual factors

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* Received for publication, Aug. 2, 1923.

[1] Ehrenfest, Hugo: Birth Injuries of the Child, New York, D. Appleton & Co., 1922.

responsible for injuries of intracranial structures during birth. Their frequent association with external traumatic lesions, their anatomic characteristics and their location, at first brought mechanical factors as the direct and immediate cause of their production into the foreground. The normal physiologic reduction of the intracranial space during molding, but especially forced and exaggerated compression in the cases of mechanical dystocia or of operative delivery (forceps and breech extraction), seemed most obviously to represent the mechanical factors responsible for the intracephalic traumatization. Further observations, however, and especially necropsy studies since the introduction of Beneke's method of opening the skull, revealed the fact, now generally accepted, that extensive destruction of structures frequently occurs also within the skulls of infants born spontaneously after easy and quick labors, and even in children delivered by cesarean section. An explanation of the intracranial trauma on the basis of mechanical influences, at least for such cases, seemed unsatisfactory. Thus, writers began to add as causative factors prematurity, syphilis, asphyxiation, and more recently, hemorrhagic diathesis. It can be admitted that possibly all of these factors in some form may enter into the etiology of the various types of intracranial birth lesions, and especially of birth hemorrhages; but more careful analysis leads to the inevitable conclusion that, in the individual case, they vary greatly among themselves in significance.

Various attempts have been made to group the cases of intracranial hemorrhage in the new-born in accordance with the supposed predominant etiologic factor. It was thought that such a division would prove of practical value for the purpose of diagnosis and treatment.

Warwick [2] proposed the following classification:

1. Traumatic cases, the result of the molding of the head in normal precipitate deliveries.

2. Congestion of stasis, with rupture of veins, in protracted or complicated labors.

3. A diseased condition of the child in intrauterine life, having no relationship to labor as such.

Warwick thought that the first division, theoretically at least, would represent the most common cause of injuries. In the second group, congestion and overdistension of veins lead directly to hemorrhage or indirectly to rapid degeneration and subsequent rupture. In the third group, the hemorrhagic disease of the new-born naturally would deserve first place.

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[2] Warwick, M.: Cerebral Hemorrhage of the New-Born, Am. J. M. Sc. **158**:95 (July) 1919.

Munro and Eustis[3] accepted this division as essentially correct, but felt that asphyxia as a cause for congestion and stasis with rupture of the cerebral veins is sufficiently important to demand special consideration. They, therefore, modified Warwick's classification thus:

1. Traumatic group: hemorrhage caused by excessive molding of the head and overriding of the sutures.
2. Asphyxia group: hemorrhage caused by excessive cerebral venous congestion with rise of intracranial pressure.
3. Fetal disease group: hemorrhage having no relation to the labor, but being most commonly caused by hemorrhagic disease and rarely by syphilis or other toxemias.

Since grouping clinical asphyxia, "an easily diagnosed condition," separately in their etiologic classification, Munro and Eustis have found that the number of cases of intracranial hemorrhage which might be properly classed as traumatic in origin has become relatively quite small. Almost as an apology for still maintaining the traumatic group in their classification, they add: "Nevertheless, as long as fracture of the skull occurs, and as long as there continues to be a tearing of the sinuses and meninges by excessive overlapping of the sutures, so long will it be necessary to classify certain of these cases as strictly traumatic in origin."

Such a statement, if accepted as correct by pediatricians, will go far in obscuring what already has been revealed by the investigations of obstetricians concerning the traumatization of intracephalic structures incident to the process of birth.

At the outset, I wish to emphasize a striking difference in the points of view of pediatrician and obstetrician. The pediatrician tends to adhere to the erroneous belief that the terms intracranial birth hemorrhage and birth injury are synonyms. This evidently is due to the fact that he sees and, therefore, becomes interested only in injuries associated with hemorrhage, the latter alone causing symptoms evident immediately after birth. The obstetrician, from the standpoint of prophylaxis, is concerned with lesions without hemorrhage as well as with those associated with extravasation of blood.

There are a few facts concerning intracranial birth lesions which may be regarded as established beyond all reasonable doubt. Among them, as bearing more specifically on the problem under discussion, I shall mention the following: In necropsies properly performed on all stillborn infants and on new-born infants dying within the first few days of life, some lesion, clearly traumatic in origin, is discovered within the skull in approximately one half of the cases. Most common among them are tears of the tentorium. In a considerable number of the cases, estimated at from 20 to 25 per cent., the intracephalic injury is not directly responsible for the death but represents merely an incidental finding. In these instances, as a rule, the lesion is accompanied by only a negligible hemorrhage or none at all. Necropsies on somewhat older infants, dying from intercurrent diseases, often reveal the remnants or evident sequelae of hemorrhages which undeniably have occurred at the time of birth. In the larger number of instances in this latter group, the history fails to show any symptoms in the new-born which would have suggested an intracranial traumatization.

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[3] Munro, Donald, and Eustis, R. S.: Diagnosis and Treatment of Intracranial Hemorrhage in the New-Born, Am. J. Dis. Child. **24**:273 (Oct.) 1922.

From these facts, we can draw at least two definite conclusions: (1) that not all intracranial birth lesions cause death or even marked symptoms in the new-born, and (2) that intracephalic injuries, sustained in birth, must occur with even greater frequency than is indicated by the postmortem findings in new-born infants.

Observations and experimental studies, extensively recorded in the literature of obstetrics, have now determined the exact mechanical factors which effect the traumatization of the meninges, especially of the dura mater.

Compression of the fetal head, resulting in a relatively small reduction of the volume of the skull, but leading to a rather marked change in its configuration, represents an integral element of every labor. Experience proves that, in general, this compression is free of any noteworthy harmful effect on the child. Under normal conditions, a process is at work which precludes a pathologic increase of intracranial pressure. As now understood, this protection of the skull contents and, most important, of the brain tissue, is procured by the escape of a small amount of cerebrospinal fluid toward the spinal canal, and furthermore by a reduction of the volume of blood within the brain.

The process of molding effects a change in the relative position of adjoining skull bones which is most pronounced in the sagittal suture. As the result of the overriding of the parietal bones, the subjacent dura is both folded and stretched. If this overlapping is excessive (mechanical dystocia) or is very suddenly accomplished (forceps extraction, large doses of pituitary extract), or if the dura is abnormally fragile (prematurity), the strained dura may break. The longitudinal sinus itself may be torn open or, as is more commonly the case, the tear may involve only the veins on one side, exactly at the site of their entrance into the sinus. If these vessels are engorged (asphyxiation, or passive congestion in the aftercoming head), they naturally will break under a relatively smaller strain. Under these conditions, obviously, the resulting hemorrhage will be more profuse. If, coincidentally, there is an abnormal delay in the blood clotting (hemorrhagic diathesis), the hemorrhage will continue, and may attain dangerous proportions, even if the tear is small and involves but a few, and those small, vessels.

In a breech extraction not properly managed, exaggerated lapping of the parietals over the squama of the occipital bone in an identical manner may cause the rupture of veins emptying into the transverse sinus, or laceration of the sinus itself, or might push the cerebellum with sufficient force against the overlying tentorium to cause its laceration.

Far more significant, however, than this overlapping of adjoining skullbones is the changed configuration of the molded head in the direct mechanical causation of meningeal lacerations. The exact mechanism of the traumatization of the tentorium, the almost typical and indeed most common form of birth injury, has been definitely established by the pioneer work of Beneke.[4] It has been fully confirmed by many other investigators, among them Eardley Holland [5] and Capon.[6] I refer readers interested in the details of the problem to my monograph,[1] or to the papers of Holland and Capon, and I wish to emphasize in this connection that the mechanical conditions leading to tentorial laceration can easily be reproduced and demonstrated on the head of a new-born infant, opened at necropsy in accordance with Beneke's suggestion (Figs. 1, 3, 4).

Compression of the head in any one direction results in the shortening of the diameter lying in the direction of the pressure, and a simultaneous compensatory lengthening of the diameter perpendicular to the one reduced. Therefore, compression of the head, during the second stage of labor, along either the anteroposterior or the lateral diameters, always leads to an increase in the length of the vertical diameters of the infant's head. The cranium becomes more convex and the falx is pulled upward. It is generally believed that certain histologic structural details of such tissues as bones or ligaments permit reliable deductions in regard to the functional purpose of these textures. The longitudinal arrangement of the fibers in the falx and their lateral extension on either side into the tentorium then would indicate that it is the chief mechanical task of the falx to prevent an abnormal extension of the long diameters of the cranium; i. e., to counteract during molding the effect of lateral compression. But sudden or excessive compression in either a lateral or a longitudinal direction, by raising the falx, would exert a definite pull at the place where the fibers of the falx diverge to either side to form the upper blade of the tentorium. This also represents the relatively weakest part of the falx and, as a matter of fact, it is the site of predilection for tentorial tears.

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[4] Beneke: Ueber Tentoriumzerreissung bei der Geburt, etc., München. med. Wchnschr. **57**:2125, 1910.

[5] Holland: Cranial Stress of the Foetus During Labor, J. Obst. & Gynec. Brit. Emp. **29**:551, 1922.

[6] Capon, N. B.: Intracranial Traumata in the New-Born, J. Obst. & Gynec. Brit. Emp. **29**:572, 1922.

Three specimens, recently obtained in the service of the obstetric department of Washington University, clearly show various points of interest and importance.

In Figure 1, the head of a small fetus, the structure of the anterior part of the falx well expresses its vulnerability. The tentorial blades are so thin that the underlying cerebellum can be seen through them. Who will doubt that these thin dura folds might easily be torn, if this head by a strong uterine contraction (perhaps induced by pituitary extract) was quickly forced through a not fully dilated cervix or through the rigid vulvar ring of a primipara? The softness and elasticity of the cranial bones of a premature fetus favor exaggerated change in configuration and thus increase the danger to the fragile dura. This assumption is well supported by a comparison with the observations made in the next case.

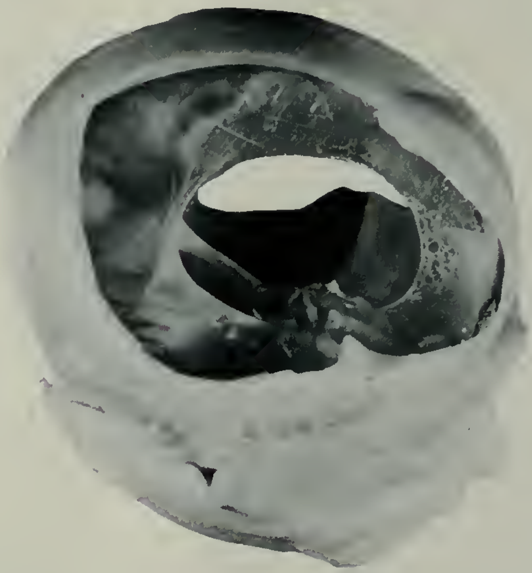

Fig 1.—Head of small fetus showing the thinness and vulnerability of falx and tentoria. Through the latter the outline of the underlying cerebellum can be seen. The fibers of the falx diverge posteriorly on either side into the upper blade of the tentorium. The head was opened after the Beneke method.

The specimen was obtained by the department from an outside physician. A futile attempt had been made to extract a very large,

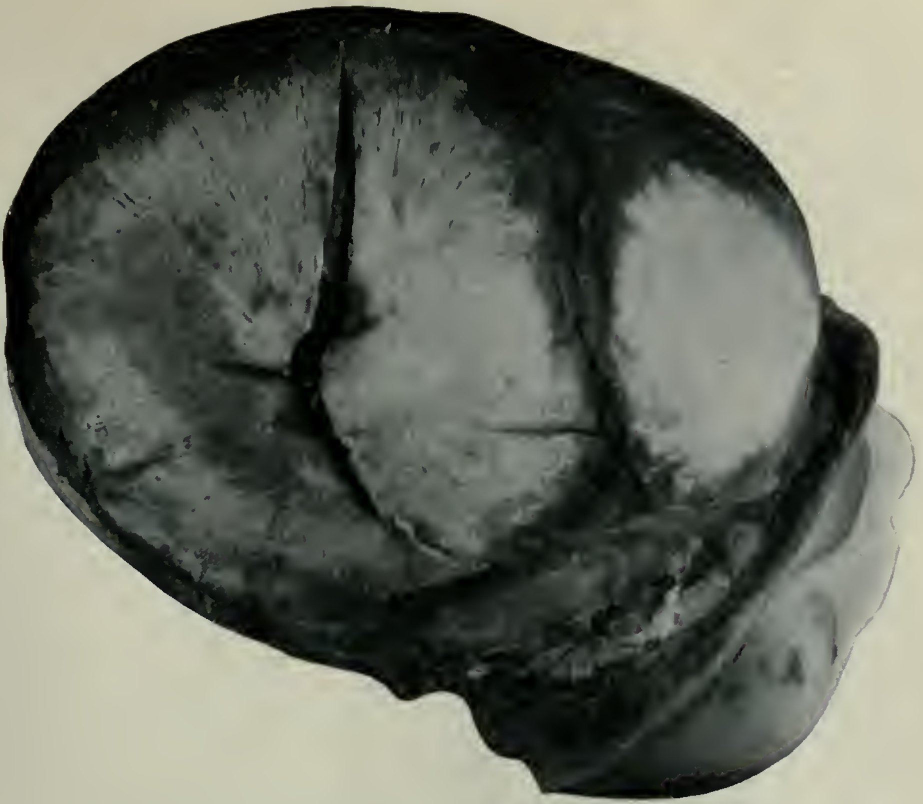

Fig. 2.—Head of a postmature fetus. The right parietal bone was fractured in an attempt at extraction by means of high forceps.

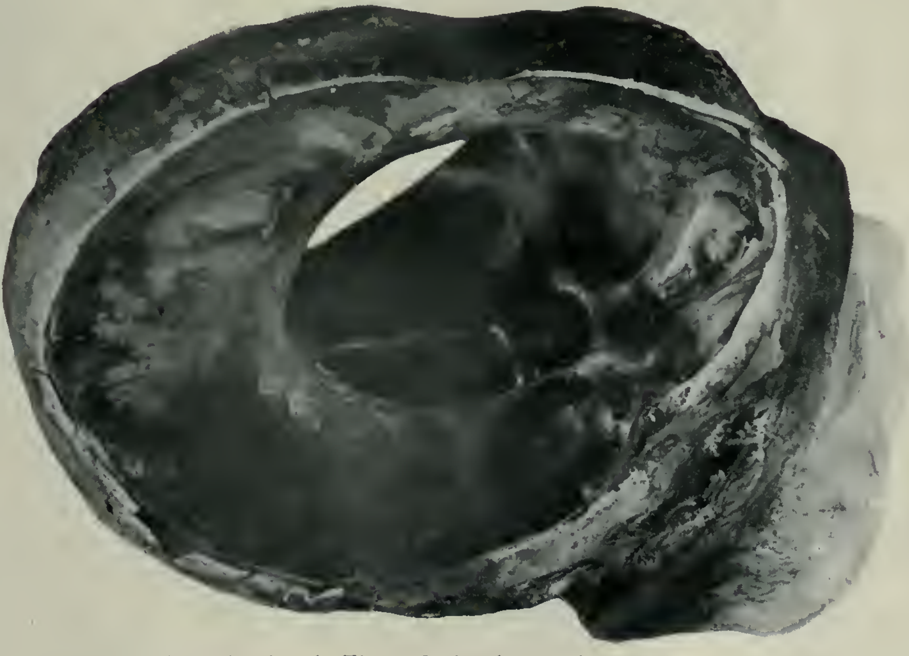

Fig. 3.—Same head as in Figure 2, showing the interior. The dura is intact. Hemorrhages between the blades of the falx can be seen.

clearly overcarried infant, by means of a high forceps. The results can be seen in Figures 2 and 3. External force proved sufficient to cause deep fractures of both parietal bones (only the right parietal is shown in Fig. 2). The hard skull bones, however, proved too rigid to permit a marked change in the configuration. Falx and both tentoria remained intact, exhibiting the effect of the very severe trauma solely in the form of small hemorrhages confined between the dura blades (Fig. 3).

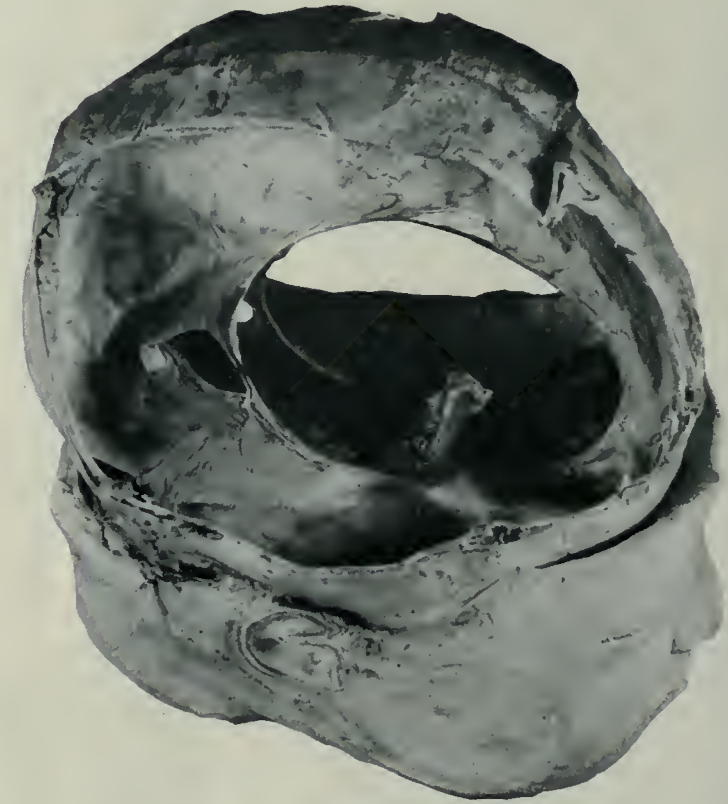

Fig. 4.—Head of full term infant, stillborn spontaneously in vertex presentation. Both tentoria are torn, the right more extensively. There is a hole in the falx, leaving the vessels crossing the opening intact. There are three distinct traumatic lesions, of which only two caused hemorrhage.

In the third skull (Fig. 4), that of a stillborn infant, spontaneously expelled, head first, the skull bones remained intact, but there was found a deep tear of the right tentorium, severing both blades, another tear through the left tentorium and an opening in the falx. This last injury is particularly instructive. While the dura tissue itself was found split, the vessels running through this area remained intact, as can be seen in the illustration. Thus, this particular opening in the falx represents an intracranial traumatic birth injury causing no hemorrhage.

An appreciation of the direct mechanical causes of tentorial tears, as already described and convincingly demonstrated in the few specimens illustrated here, would seem to render entirely acceptable the assertion of some authors, that meningeal injuries may be the result of unskilful manipulations during resuscitation; e. g., of too firm a fixation of the infant's head between the wrists during swinging after Schultze's method; or that they might be produced near the end of the second stage of a normal and spontaneous labor, when the attendant presses the occiput of the fully rotated head too forcibly toward the symphysis in an effort to protect the perineum against injury. Serious intracranial hemorrhages have been recorded in infants delivered by cesarean sections. In some of these cases, the traumatization undeniably occurred before operation as the result of the effort of the uterus to force the relatively too large fetal head into the narrowed pelvic inlet. In other instances, in which operation was actually performed before the onset of labor, the infant's head evidently was severely traumatized solely by its forced extraction through a uterine incision of insufficient length.

The obstetrician, thoroughly familar with such facts, must disagree with Monro and Eustis that intracranial birth hemorrhages are but rarely traumatic in origin.

These authors proclaim asphyxiation as the most common etiologic factor in such hemorrhages. They write:

> At birth, clinically asphyxiated babies are cyanotic, do not start breathing well, or cry, and require treatment which is directed toward the artificial stimulation of respiration. It has also been repeatedly observed that these clinically asphyxiated babies, when they die, die from respiratory failure, the heart continuing to beat for some time after the respiratory center has definitely ceased to function, and after it will no longer react to artificial stimulation. Until this clinical evidence can be disproved by chemical studies of the blood of the new-born infant, therefore, we must consider the baby exhibiting the above symptoms as asphyxiated.

One cannot resist the temptation to add: "If there is no necropsy in such a case, the diagnosis asphyxia will be given as the cause of death in the death certificate; but if there is a necropsy, in the overwhelming majority of these cases an intracranial hemorrhage will be found; and the cause of death should have been given as traumatic intracranial birth injury." In all cases of severe birth hemorrhage, the baby, if born alive, is asphyxiated. I maintain that every baby born seemingly asphyxiated should be considered as possibly suffering from an intracranial traumatization, and, therefore, should not be subjected to any violent efforts at resuscitation, because such manipulations might in themselves aggravate the hemorrhage just enough to cause the death of the infant. It is unfortunate that we are unable to differentiate in the new-born a true asphyxia, the result of mechanical interference with oxygen supply, from the clinical picture of asphyxiation, brought on by the traumatization of the breathing center.

The undisputed fact that the overwhelming majority of babies, found at postmortem to have succumbed to an intracephalic hemorrhage, after birth were cyanotic and did not breathe properly, cannot be adduced as proof of the great importance of asphyxia as the direct cause of such hemorrhages. Of no more value in this respect is the often emphasized fact that small petechial hemorrhages, generally considered as characteristic of asphyxiation, are found in the various serosae of these infants. This is not surprising since these babies died in a state of asphyxiation resulting from the improper function of the breathing center. The one question under discussion is whether the asphyxia is responsible for the intracranial hemorrhage, or the intracranial hemorrhage for the asphyxia. I am not aware of the fact that asphyxiation in young children commonly, if ever, causes the rupture of meningeal veins or of a large sinus merely from overdistention. It then seems unreasonable to insist on this particular mechanism for the rupture of intracranial vessels in the course of birth simply on theoretical grounds, with the added necessity of disregarding deliberately the factor of the compression of the head, a factor unquestionably of a traumatic nature and present in the second stage of every labor. However, it can be readily admitted that a passively congested vein or sinus of a deeply asphyxiated infant is more liable to rupture under external pressure or strain.

The effect of a meningeal tear on the infant in the main is determined by the hemorrhage resulting from it. The occurrence of a hemorrhage and the size of the hematoma, therefore, actually depend on whether any vessels are torn and whether they are small or large, empty or full. Thus, asphyxiation enters into the problem of intracranial birth hemorrhages, but only as a predisposing and contributory cause, and not as the direct cause of the injury. Asphyxiation positively cannot have any bearing on the fact that so often in labor the tentorium is torn.

As a third etiologic factor, Warwick, Munro and Eustis and many others emphasize hemorrhagic diathesis. It is impossible to establish any immediate relation between this disease and lacerations of the dura mater *per se*. While this anomaly of the blood undeniably is responsible for certain fairly common types of hemorrhage from various mucosae of the new-born, I cannot see how it could be adduced as an acceptable explanation of hemorrhages evidently resulting from the rupture of a sinus or vein within the skull, again with utter dis-regard of the mechanical factor of compression of the head during the process of molding. Nevertheless, it must be admitted that hemorrhagic diathesis also plays some rôle in the etiology of intracranial birth hemorrhages, even more important than asphyxia, but again only as a contributory factor. If the blood coagulation time is greatly increased, the unduly prolonged extravasation of blood even from a very small vessel will finally prove as disastrous as the rupture of a large vessel in another infant with normal coagulation time. The very gradual formation of the hematoma under these conditions explains the not uncommon appearance of the first manifest symptoms of an intracranial injury only some time after birth.

I should like to call attention in this connection to the seemingly conclusive experiments and investigations of Evarts A. Graham [7] concerning the pathogenesis of the hemorrhagic diseases. He established the fact that all those conditions of the new-born which are characterized by a hemorrhagic tendency most probably are the result of a deficiency in oxidation, and can be experimentally produced by chloroform as well as by direct asphyxiation. These, indeed, are findings of far-reaching importance in clearing up some of the obscurer points in the etiology of intracranial birth hemorrhages and their relation to asphyxiation and hemorrhagic diathesis.

Syphilis and the toxemias of pregnancy, which are cited as direct causes of birth hemorrhages, can be accepted only as predisposing factors. Any disease which tends to lead to the premature termination of pregnancy is of etiologic significance because all structures of the immature fetus, and especially those within the skull, admittedly are very fragile and vulnerable. As far as the toxemias are concerned, the fact furthermore must be borne in mind that they frequently call for the termination of labor by artificial and forcible means, which notoriously augment the direct mechanical dangers to the fetal head.

In the light of our present information, it seems best to differentiate accurately between the *direct mechanical* and the *predisposing* and *contributary factors* in the causation of intracranial birth injuries in general, and of birth hemorrhages in particular. The etiology of intracranial injuries sustained in birth might be described briefly thus: The meninges and the brain substance itself might be traumatized by severely injured skull bones (indentations, depressed fractures). More often, in the absence of any evidence of an external injury, a dura fold is torn as the result of a severe strain if molding is excessive or suddenly accomplished. Such mechanical traumatization of the meninges, therefore, most often is observed in difficult labors and those terminated artificially. But the physiologic trauma also, incident to a spontaneous and seemingly normal birth, might be sufficient to cause the laceration of parts of the dura mater and, with them, of a sinus or veins, in the presence of such predisposing factors as prematurity or marked congestion. Contributory factors in the formation of the hematoma are congestion and hemorrhagic disease, more indirectly also certain reprehensible methods of resuscitation of the seemingly asphyxiated new-born infant.

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[7] Graham, E. A.: Pathogenesis of the Hemorrhagic Diseases of the New-Born, J. Exper. Med. **15**:307, 1912.

A grouping of the various etiologic causes of intracranial birth injuries in this manner does not in the least detract from its value as an aid in diagnosis or treatment, but unquestionably is of greater advantage in the more important problem of their prevention.

Emphasis properly belongs on those primarily mechanical factors which cause intracranial structures to be crushed or torn, with more or less hemorrhage resulting from the injuries. The frequency with which such injuries involve more than one structure within the cranium (e. g., both tentoria and falx in the case shown in Fig. 4) well accounts for the perplexing symptomatology and the futility of surgical interference in many of the cases.

Metropolitan Building.

THE DEVELOPMENTAL TOPOGRAPHY OF THE LARYNX, TRACHEA AND LUNGS IN THE FETUS, NEW-BORN, INFANT AND CHILD *

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The development of the respiratory system in the embryonic period of man has been carefully worked out by a number of observers and the features of the process are well known. On the other hand, the development of this system from the third fetal month to birth, in early infancy, later infancy and childhood has received little attention. The present report is a study of the topographic relationships of the larynx, trachea and lungs, with especial emphasis on the changes in this relationship during the entire developmental period. All the available data on the subject, for infancy, childhood and adult life, have been correlated with my findings in the fetus, the new-born infant and the child. It is hoped that in this way a picture may be sketched of the relation of the parts of the respiratory system to the vertebral column, beginning with early fetal life and ending with maturity.

A few observations in addition to those mentioned above have also been made and recorded. These include the lobation of the lungs, the development of the cardiac notch, the angle that each bronchus makes with the midsagittal plane and the relation of the apices of the lungs to the suprasternal notch. A study of the lineal growth of the component parts of the respiratory system was also made in conjunction with the present paper, but the results of that study will be reported separately.

MATERIAL AND METHODS OF COLLECTING DATA

The material used in this study consisted of 102 fetuses and full-term new-born children, ranging in crown-heel or total body length from 10 to 55 cm.; midsagittal sections of a 5 year and an 8 year old child; a model of the topography of the thoracic and abdominal viscera of a 65 mm. human embryo, and a series of tracings of medially sectioned human fetuses. The major part of the material forms part of the collection of the Institute of Anatomy of the University of Minnesota; the remainder is part of the collection of the Department of Anatomy of the Medical College of Virginia. Eighty-two of the fetuses were stillborn and twenty-two were infants in whom respiration had been partially established, as indicated by the condition of the lungs. The fetuses and full-term infants were preserved by intravascular injection of an

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* From the departments of anatomy of the University of Minnesota and of the Medical College of Virginia.

aqueous solution of 10 per cent. formaldehyd and 1 per cent. chromic acid. No material in which pathologic conditions were macroscopically observable was used in this study.

The material was prepared in the following manner:

> The skin, muscles, etc., were dissected from the anterior of the neck and thorax; the clavicles and costal cartilages were cut along the anterior axillary line, and the anterior part of the thoracic cage was then removed. The infrahyoid muscles, thyroid gland, thymus, heart and great vessels were next carefully dissected out, leaving the larynx, trachea, bronchi and lungs fully exposed in situ. The chin was always held in a horizontal position in order to avoid elevation or depression of the larynx and trachea due to overextension or depression of the head.
>
> The thyrohyoid membrane was next cut in order to make visible the tip of the epiglottis, which was taken as the superior limit of the larynx. A pin was then inserted into the vertebral column to mark the level of the tip of the epiglottis. The inferior vertebral level of the larynx was marked by a pin at the level of the inferior margin of the cricoid cartilage. A pin was inserted into the vertebral column on each side at the apex of each lung in order to determine its uppermost level. Pins were similarly placed at the most inferior level of each lung. Later, when the heart was removed, the vertebral level of the tracheal bifurcation was marked by a pin inserted into the vertebral column.

The following observations were made and recorded from each individual:

1. Crown-heel length, or total body length, from the vertex of the head to the base of the heel.
2. Crown-rump length, or sitting height, from the vertex of the head to the tip of the coccyx.
3. Vertebral level of the tip of the epiglottis.
4. Vertebral level of the inferior margin of the cricoid cartilage.
5. Vertebral level of the bifurcation of the trachea.
6. Relation of the apices of the lungs to the suprasternal notch.
7. Vertebral level of the apex of the right lung.
8. Vertebral level of the apex of the left lung.
9. Vertebral level of the most inferior part of the inferior margin of the right lung.
10. Vertebral level of the most inferior part of the inferior margin of the left lung.
11. Angle formed by the right bronchus with the midsagittal line.
12. Angle formed by the left bronchus with the midsagittal line.
13. Number of lobes and irregularities of fissures in the right lung.
14. Number of lobes and irregularities of fissure in the left lung.
15. Greatest depth of the cardiac notch.

In order to determine the vertebral levels of the several structures and organs, the vertebral column was split in its midline and the levels of the insertions of the pins were observed and recorded.

THE LITERATURE

The changes in topography of different parts of the human respiratory system in the developmental period have received considerable attention from several investigators, although apparently all the levels here presented have not been considered together in any single study in the past. The relation between the trachea, lungs, thymus and heart in fetal life and in the new-born was discussed in a previous paper.[1] There are several illustrations in the literature of midsagittal sections of fetuses [2] and new-born infants,[3] from which the laryngeal levels may be obtained. All of these which I have found have been plotted against total body length as was done in my own cases. These are shown in Figure 4, along with the data in the literature for these levels obtainable for infancy,[4] childhood,[5] and adult life.[6]

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1. Noback, G. J.: A Contribution to the Topographic Anatomy of the Thymus Gland, with Particular Reference to Its Changes at Birth and in the Period of the New-Born, Am. J. Dis. Child. **12**:120 (Aug.) 1921.

2. Ballantyne, J. W.: An Introduction to the Diseases of Infancy, Edinburgh, 1891, pp. 56-57. Cheivitz, J. H.: A Research on the Topographical Anatomy of the Full-Term Human Fetus in Situ, Copenhagen, 1899, pp. 14-16. Keibel and Mall: Human Embryology, Philadelphia, 1910, Vol. 2, p. 402, Mehnert, E.: Ueber Topographische Altersveränderungen des Atmungsapparats, Jena, 1901. Merkel, F.: Menschliche Embryonen verschiedenen Alters auf Medianschnitten untersucht, Göttingen, 1894. Scammon, R. E.: Private collection, University of Minnesota Department of Anatomy. Symington, J.: On the Relation of the Larynx and Trachea to the Vertebral Column in the Fetus and Child, Edinburgh M. J. **26**:913, 1881.

3. Birkenbusch: Die inneren Proportionen des menschlichen Halses in den verschiedenen Lebensaltern, Dissertation, Göttingen, 1890. Jackson, C. M.: On the Developmental Topography of the Thoracic and Abdominal Viscera, Anat. Rec. **3**:361, 1909. Merkel, F.: Handbuch der topographischen Anatomie, Braunschweig, 1899, Vol. 2, p. 405 (Fig. 70). Mettenheimer, H.: Ein Beitrag zur topographischen Anatomie der Brust Bauch und Beckenhöhle des neugeborenen Kindes., Morph. Arbeiten **3**:301, 1893. Piersol, G. A.: Human Anatomy, Philadelphia 1908, p. 1828. Ribemont, A.: Recherches sur l'anatomie topographique du fetus, 1878, Thèse, Paris, No. 203. Rudinger, F.: Topographisch-chirurgische Anatomie des menschen, Atlas, Stuttgart, 1873, Plate 4, Figure a.

4. Engel, St.: Form, Lage und Lageveränderungen des Bronchialbaumes im Kindesalter, Arch. f. Kinderh. (Festschrift f. Baginsky) **60-61**:267, 1913. Jackson, C. M.: Private collection, University of Minnesota Department of Anatomy. Symington, J.: The Topographical Anatomy of the Child, Edinburgh, 1887, (Plates 1 and 2).

5. Dwight, T.: Frozen Sections of a Child, New York, 1881, p. 15, Plate 3. Gedgowd, V. A.: Anatomical Peculiarities of the Respiratory Organs in Children, Dissertation, St. Petersburg, 1900, pp. 178, Plate 1 (Russian). Sluka, E.: Ueber Roentgenbefunde bei tuberculösen Kindern mit expiratorischen Keuchen, Wien. klin. Wchnschr. **23**:156, 1910. Zuckerkandl, E.: Atlas der topographischen Anatomie des Menschen, 1899, p. 163, Figure 170.

6. Corning, H. K.: Lehrbuch der topographischen Anatomie, Ed. 10 and 12, Munich and Wiesbaden, 1920, p. 202, Figure 164. Cunningham: Textbook of Anatomy, Ed. 4, 1913, p. 1077. Gray-Lewis: Anatomy of the Human Body, 1920, Philadelphia, p. 1084. Hyrtl, J.: Lehrbuch der Anatomie des Menschen,

(Footnote 6 continued on next page)

The most comprehensive study of the topographical changes of the human respiratory system is that of Mehnert (1901).[7] His study includes the literature on the subject up to that time, not only for fetal life but also for all stages through senility in postnatal life. The prenatal material which he personally studied was somewhat limited in that the epiglottis was not considered and that his cases of fetuses and new-born infants numbered only ten in addition to seven cases of Merkel and one case of Disse, or a total of eighteen. He considered the following levels: cricoid cartilage, tracheal bifurcation and the inferior margin of the lungs; all of which, with the addition of the epiglottis and the superior limit of the lungs in relation to the sternal notch and to the vertebral column, were also utilized in the present study.

Mehnert concludes that there is a definite descent with age, but states that the fetal cricoid level is similar to that in the new-born. He finds marked variation in the fetal levels of the cricoid and states that this level shows no marked tendency upward or downward but rather an oscillation. This, he believes, may be partly due to the varying position of the heads in the different cases studied, but he says that the differences in this level should be regarded as individual variations. The level of the inferior margin of the cricoid cartilage in the new-born also varies markedly according to the data of several other investigators and the one case of his own.

Mehnert's conclusions regarding the vertebral level of the tracheal bifurcation are similar to those regarding the level of the larynx. Here, again, he had ten cases of his own and seven cases of other investigators. He states that there are as great variations in this level in some fetal months as are found in his whole series, and that therefore the wide fluctuations should be regarded as individual variations. The level of the bifurcation in the trachea in the new-born he finds to be lower than that in the fetus. The explanation of this, he believes, lies in the fact that, in the fetus, the trachea is craniad to the viscera; whereas, in the new-born,

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Wien, 1889. Joessel, J.: Lehrbuch der topographischen chirurgischen Anatomie, Bonn, Ed. 2, 1899. Luschka, H.: Die Anatomie der Brust des Menschen, Tübingen, 1863, p. 463. Morris-Jackson: Text-Book of Human Anatomy, Ed. 6, Philadelphia, 1921, p. 1254. Potter, Peter: Topography of the Thorax and Abdomen, University of Missouri Studies, Science Series, Vol. 1, No. 1, Columbia, Mo., 1905. Poirer et Charpey: Traité d'anatomie humaine, Paris, 1901, Vol. 3, p. 402 and Figure 203. Quain's Elements of Human Anatomy, London, 1914, Vol. 2, Part 2, p. 152. Rauber-Kopsch: Lehrbuch der Anatomie, Leipzig, 1911, Ed. 9, No. 4, p. 190. Spalteholz, W.: Atlas der Anatomie des Menschen, Leipzig, 1920, p. 480, Figure 516. Testut, L.: Traité d'anatomie humaine, Paris, 1911, Vol. 3, p. 763, Figure 676. Testut et Jacob: Traité d'anatomie topographique, Paris, 1909, p. 629. Toldt, C.: Anatomischer Atlas, Ed. 6, Vol. 4, p. 483, Figure 813.

7. Mehnert: Footnote 2, fourth reference.

it is caudad, and therefore has the weight of the viscera pulling it downward.

According to Mehnert, the level of the larynx and of the tracheal bifurcation show no definite descent during prenatal life, but between early fetal life and maturity there is a descent in these levels of a distance represented by five vertebrae. The inferior margins of the lungs in this period of time also undergo a descent which he measures by two intercostal spaces.

Jackson,[8] in whose private collection are a number of drawings of midsagittal sections of specimens in the Leipsic Museum, furnishes levels of the epiglottis and larynx of the two new-born infants and of a 2-day-old child.

Merkel (1894)[9] illustrates and describes several embryos, fetuses, one new-born child, and an adult in midsagittal section. The levels of the epiglottis and cricoid in all of these were taken off and used in this study. Merkel believes that even though the trachea extends lower in the new-born than in the embryo, the relative increase in tracheal length is more apparent than real and that this is due to slackening in growth of the vertebrae in late fetal life.

Symington (1885)[10] states that, in the new-born, the larynx and trachea terminate at a higher level than in the adult, but he was unable to find any definite statement as to their precise position in relation to the vertebral column. He found the larynx terminating opposite the middle of the fourth cervical vertebra and the trachea at the level of the lower border of the second thoracic vertebra; and he records the levels of the upper and lower limits of the larynx and of the bifurcation of the trachea in fetuses of 4, 6 and 7 months.

Scammon,[11] in his collection, has drawings of midsagittal sections of fetuses of the following crown-rump measurements: 34.7 mm., 43.3 mm. and 26.8 mm. These measurements, as all other measurements given in the literature as crown-rump alone, were converted to crown-heel measurements by the use of the formula which I [12] devised in 1921. The data from these three fetuses are used in this study.

Ballantyne (1891)[13] records the vertebral levels of the larynx of two 7 months, one 8 months and two 9 months fetuses, as well as of one new-orn child, and an adult in midsagiital section. The levels of the neck in the new-born than in the adult. He says, "In all probability, in the case of the new-born infant with head erect, the larynx normally extends from a point opposite to the cartilage between the body and odontoid process of the axis to the level of the upper border of the fifth cervical vertebra, or to that of the disc between it and the fourth cervical vertebra. The descent of the larynx would seem, from Symington's measurements, to be a gradual process going on throughout childhood." The trachea, according to Ballantyne, lies at a higher level in the body of the infant than in the adult. He gives its limits as extending from the body of the fifth cervical to the body of the third thoracic vertebra. Birkenbusch (1890)[14] records the vertebral levels of the larynx in the case of two new-born infants.

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[8] Jackson: Footnote 3, second reference; Footnote 4, second reference.

[9] Merkel: Footnote 2, fifth reference.

[10] Symington: Footnote 2, seventh reference; Footnote 4, third reference.

[11] Scammon: Footnote 2, sixth reference.

[12] Noback, G. J.: Simple Methods of Correlating Crown-Rump and Crown-Heel Lengths of the Human Fetus, Anat. Rec. **23**:241, 1921.

[13] Ballantyne: Footnote 2, first reference.

Ribemont (1878)[15] illustrates a midsagittal section of a stillborn child in which the tip of the epiglottis is at the level of the lower border of the atlas and the inferior margin of the cricoid at the level of the middle of the fourth cervical vertebra.

Rudinger (1873)[16] pictures a midsagittal section of a new-born child in which the laryngeal levels are discernible.

The vertebral levels of the larynx and of the trachea in infancy and childhood have not been considered by many investigators. Symington (1887)[17] records these levels in infants 3½, 4, 6, 8 and 12 months, and in children 1 year and 10 months, 2 years and 2 months, 5 years, 6 years and in one child of 12 years. In another contribution, Symington (1881)[18] illustrates a midsagittal section of a 2 year old child in which he finds that the inferior margin of the cricoid cartilage is opposite the lower border of the fourth cervical vertebra and that the tracheal bifurcation is opposite the first thoracic vertebra. Symington concludes that the cervical part of the spinal column increases in length at a rate similar to the increases in length of the larynx, and that consequently the high position of the larynx in the neck of the child, as compared with the adult, cannot be due to its relatively small size. Symington's data are recorded in Chart 4.

Mettenheimer (1893)[19] records the levels of the inferior margin of the larynx and tracheal bifurcation in three new-born infants, and Chievitz (1899)[20] the levels of the epiglottis and larynx in two new-born children.

Birkenbusch (1890)[14] lists the vertebral levels of larynx and tracheal bifurcation in three children, 1, 6 and 13 years old, respectively.

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[14] Birkenbusch: Footnote 3, first reference.
[15] Ribemont: Footnote 3, sixth reference.
[16] Rudinger: Footnote 3, seventh reference.
[17] Symington: Footnote 4, third reference.
[18] Symington: Footnote 2, seventh reference.
[19] Mettenheimer: Footnote 3, fourth reference.
[20] Chievitz: Footnote 2, second reference.

Sluka (1909),[21] after pouring Wood's metal into the trachea, determined the vertebral level of the bifurcation of the trachea by means of the roentgen ray. He concluded that the level of the tracheal bifurcation, without exception, in children between 1 and 4 years, was at the fourth thoracic vertebra; i. e., at the same level as in the adult.

Piersol (1908)[22] has an illustration which shows the tracheal bifurcation in a 2-year-old child as at the level of the fifth thoracic vertebra.

Dwight (1881)[23] says, "the bifurcation of the trachea is seen opposite the lower border of the fourth dorsal vertebra. This is practically its adult position in regard to the spine." The child described was 3 years old.

Zuckerkandl (1904)[24] illustrates a midsagittal section of a 7-year-old child in which the inferior margin of the larynx is opposite the sixth cervical vertebrae and the tracheal bifurcation between the fourth and fifth thoracic vertebrae.

The most extensive work on the level of the tracheal bifurcation in infancy and childhood is that of Engel (1913)[25] who made a roentgen-ray study of 112 living children between 2 and 8 years of age. He found that, after the second year, the levels, though fluctuating, remain practically uniform.

Keibel and Mall (1910)[26] state that the larynx is much higher in the embryo and in the fetus than in the adult, and that at the time of birth the descent of the larynx is not yet completed.

Gedgowd (1900)[27] concluded that the growth of the larynx and trachea, in childhood, corresponds more to the growth of the trunk and neck than to that of the body.

The vertebral levels of the lungs of fetus and infant are barely mentioned in the literature, practically the only reference to these levels being found in an article by Jackson (1909),[28] who says, "The lungs of the 11 millimeter embryo correspond approximately to the position later of the lung apex, lying opposite the last cervical and the first two thoracic segments . . . The migration continues downward along the vertebral column, however, so that the lung in the 17 millimeter embryo lies opposite the 4th-9th thoracic vertebrae. In the 31 millimeter embryo it is opposite the 1st-10th thoracic vertebrae and in the 65 millimeter it lies opposite the 2nd-11th thoracic vertebrae." Jackson's lengths are crown-rump, and have been converted into crown-heel, for use in this study, by my method.[12]

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[21] Sluka: Footnote 5, third reference.
[22] Piersol: Footnote 3, fifth reference.
[23] Dwight: Footnote 5, first reference.
[24] Zuckerkandl: Footnote 5, fourth reference.
[25] Engel: Footnote 4, first reference.
[26] Keibel and Mall: Footnote 2, third reference.
[27] Gedgowd: Footnote 5, second reference.
[28] Jackson. Footnote 3, second reference.

Jackson,[29] in his personal collection, has drawings of a posterior dissection of 5 day old child, made by J. A. Watkins. These show the levels of the right lung to be between the middle of the first and the middle of the tenth thoracic vertebrae, and the levels of the left lung to be between the middle of the first thoracic and the upper border of the eleventh thoracic vertebrae.

All the data mentioned in the foregoing, with the addition of two of my specimens from children, aged 5 and 8 years, respectively, are recorded in Chart 4. Included in this illustration for the purpose of comparison are the vertebral levels of the larynx and trachea of the adult as given in texts and atlases.[6]

The observations on the levels of the larynx are more numerous, owing to the number of levels that have been obtained from the illustrations of midsagittal sections. There is a range of variation in these data because different observers studied individuals whose heads were in various postures; in some cases, the head was extended; in others, it was depressed, with a consequent influence on the levels of the larynx. In my series of cases, the head was always held in the same position; i. e., so that the inferior margin of the lower jaw was at a right angle to the long axis of the body. Taken as a whole, the levels of the larynx and trachea, except for this wide variation, coincide quite closely with the results obtained by me. This may be seen on comparing Charts 3 and 4.

The material in the literature for the period of infancy is rather meager, but, as is seen in Chart 4, these data indicate that the levels of the larynx and trachea are practically the same as those in late fetal life. This continuation of similar relationship of a group of organs to the body as a whole in both fetal life and early infancy is in agreement with the conclusions of Scammon (1922),[30] who has projected the fetal weight growth curves of many organs for several months after birth, and finds that the relative increase in weight in fetal life continues through approximately the first nine months of postnatal life.

The data for childhood are also quite meager, as is indicated by their number in Figure 4. However, in spite of the small number of cases, it is evident that, during later childhood, there is a distinct descent of the levels of the larynx and also a drop in the level of the tracheal bifurcation, which begins earlier than that of the larynx.

The data for the levels of the epiglottis, inferior border of the cricoid cartilage and of the bifurcation of the trachea are also plotted in Figure 4. In the case of the adult, we find, as in earlier life, that there are few definite data. The observations recorded in the plot are from statements and illustrations in the literature. Each level observed ranges over the distance represented by three vertebrae and two disks.

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[29] Jackson: Footnote 4, second reference.

[30] Scammon, R. E.: On the Time and Mode of Transition from the Fetal to the Postnatal Phase of Growth in Man, Anat. Rec. **22**:34, 1922.

OBSERVATIONS AND CONCLUSIONS

(*a*) *Topography of larynx, trachea and lungs during fetal life, infancy, childhood and adult life.*—The relation of the respiratory system to the vertebral column and the shifting of this system in a craniocaudal direction was studied by locating the levels of the following points: the tip of the epiglottis, the inferior margin of the cricoid cartilage, the tracheal bifurcation, the upper and lower limits of the lungs and the relation of the apex of each lung to the suprasternal notch. These levels were determined from my material on prenatal life, the new-born and two cases in children of 5 and 8 years, respectively. The literature was then examined and all available data regarding the levels of these points in the respiratory system were obtained as were also the data for infants, children and the adult.

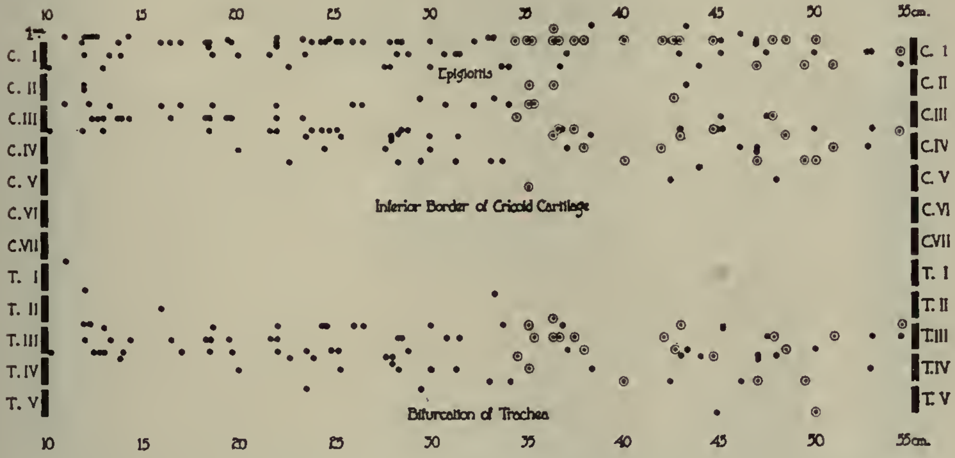

Chart 1.—Vertebral levels of the epiglottis, inferior border of the cricoid cartilage and the bifurcation of the trachea during fetal life and in the period of early infancy.

The data obtained from my material was plotted on graph paper and are reproduced in Charts 1 to 7, inclusive.

Chart 1 presents the vertebral levels of the tip of the epiglottis, inferior margin of the cricoid cartilage and the tracheal bifurcation during prenatal life and in the new-born as determined by me. The level of the epiglottis in relation to the vertebral column has a slight variation but is limited to a span of a few millimeters superior to or inferior to the first cervical vertebra. The range of the level of the tip of the epiglottis is therefore limited to a distance which may be regarded as equivalent to not more than one vertebra and intervertebral disk.

The descent of the epiglottis throughout the course of life from early prenatal to adult life is apparently as follows: The level is practically constant during prenatal life and infancy (Charts 1 and 4); a drop of two vertebrae and disks occurs between the first and thirteenth years, and a very slight descent occurs after this time, the level in the adult being quite constant.

The level of the inferior margin of the cricoid cartilage, and therefore of the inferior limit of the larynx, is less constant during fetal life and early infancy than is that of the epiglottis. In the 10 to 15 cm. group, it is located in the vicinity of the third cervical vertebrae; whereas, in the 45 to 50 cm. group, it has dropped to the vicinity of the fourth cervical vertebra. The descent is marked at all body lengths by wide variations, but as a whole it is a rather gradual one. The total drop between early fetal life and in early infancy is about equivalent to one vertebra and disk.

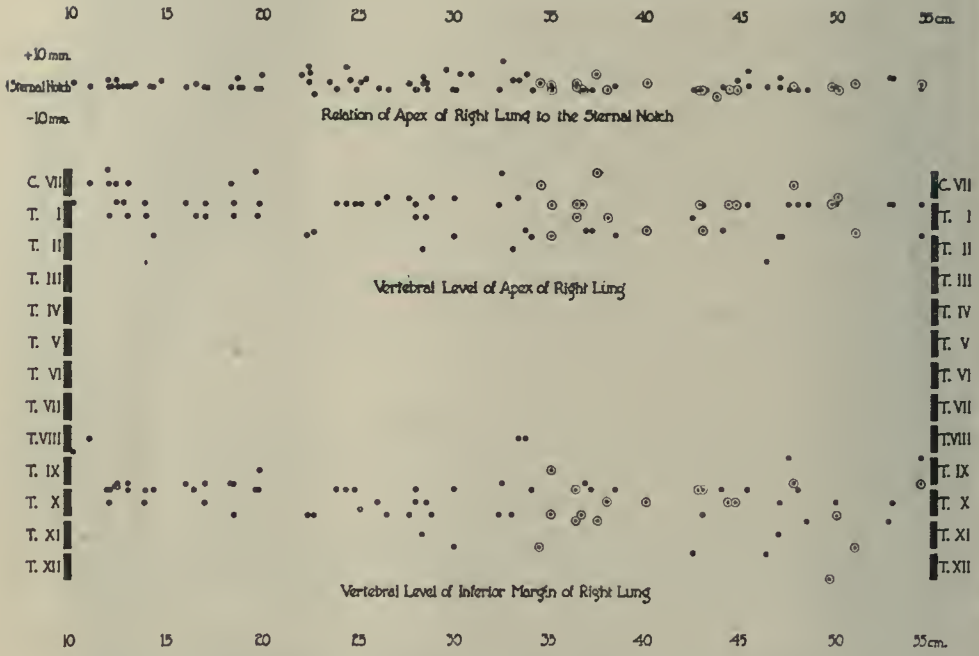

Chart 2.—The relation of the apex of the right lung to the suprasternal notch in the fetus and the new-born; the vertebral levels of the apex and of the inferior margin of the right lung.

The descent of the inferior margin of the larynx considered from early fetal through adult life begins in the fourth fetal month and continues until birth (Chart 1), a drop of about one vertebra and one disk.

This level is maintained during infancy, but another descent occurs during childhood (Chart 4), so that by the thirteenth year the inferior margin of the cricoid cartilage has descended about two vertebra and one disk, opposite to the vicinity of the sixth cervical vertebra. The adult data indicates that there is a further descent of one vertebra and disk, to the seventh thoracic vertebral level.

The level of the tracheal bifurcation in the fetus and during the period of the new-born is also less constant than the level of the epiglottis. In the 10-15 cm. group, the average level is at the third thoracic vertebra, and in the 45-50 cm. group, around the third and fourth thoracic vertebrae. There is, therefore, an appreciable descent in prenatal life of an extent of one vertebra and one intervertebral disk. The descent, as in the case of the lower margin of the larynx, is gradual from early fetal life to the end of the prenatal period.

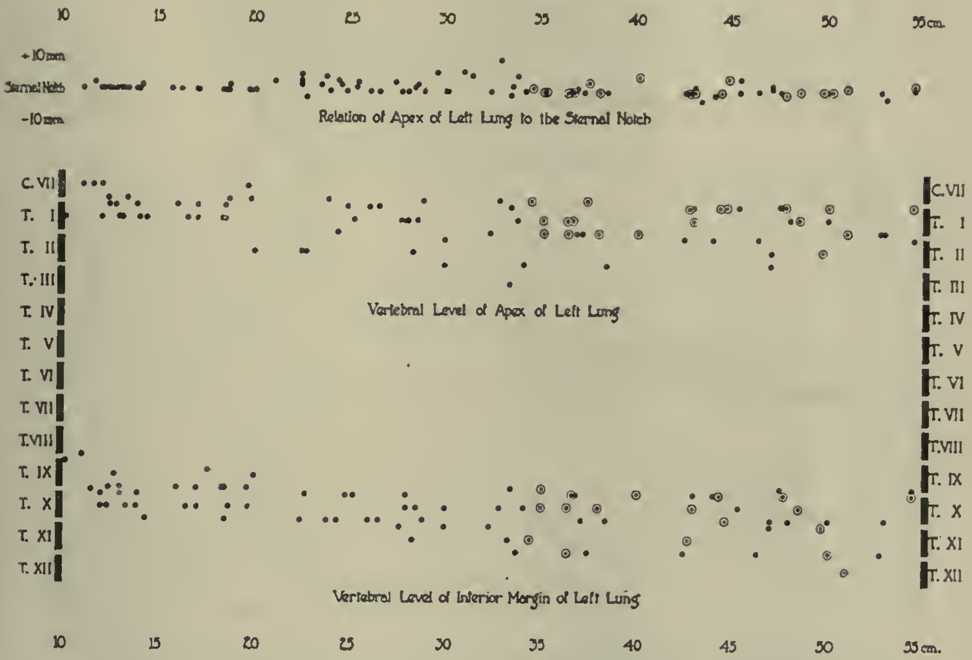

Chart 3.—The relation of the apex of the left lung to the suprasternal notch in the fetus and in the new-born; the vertebral levels of the apex and of the inferior margin of the left lung.

The bifurcation of the trachea considered from early fetal life through infancy, childhood and adult life (Charts 1 and 4) is as follows: Like the lower limit of the larynx, it begins a descent in the fourth fetal month from the level of the third thoracic vertebra to a region between the third and fourth thoracic vertebrae at birth. This level persists during the period of infancy, but early in childhood, at

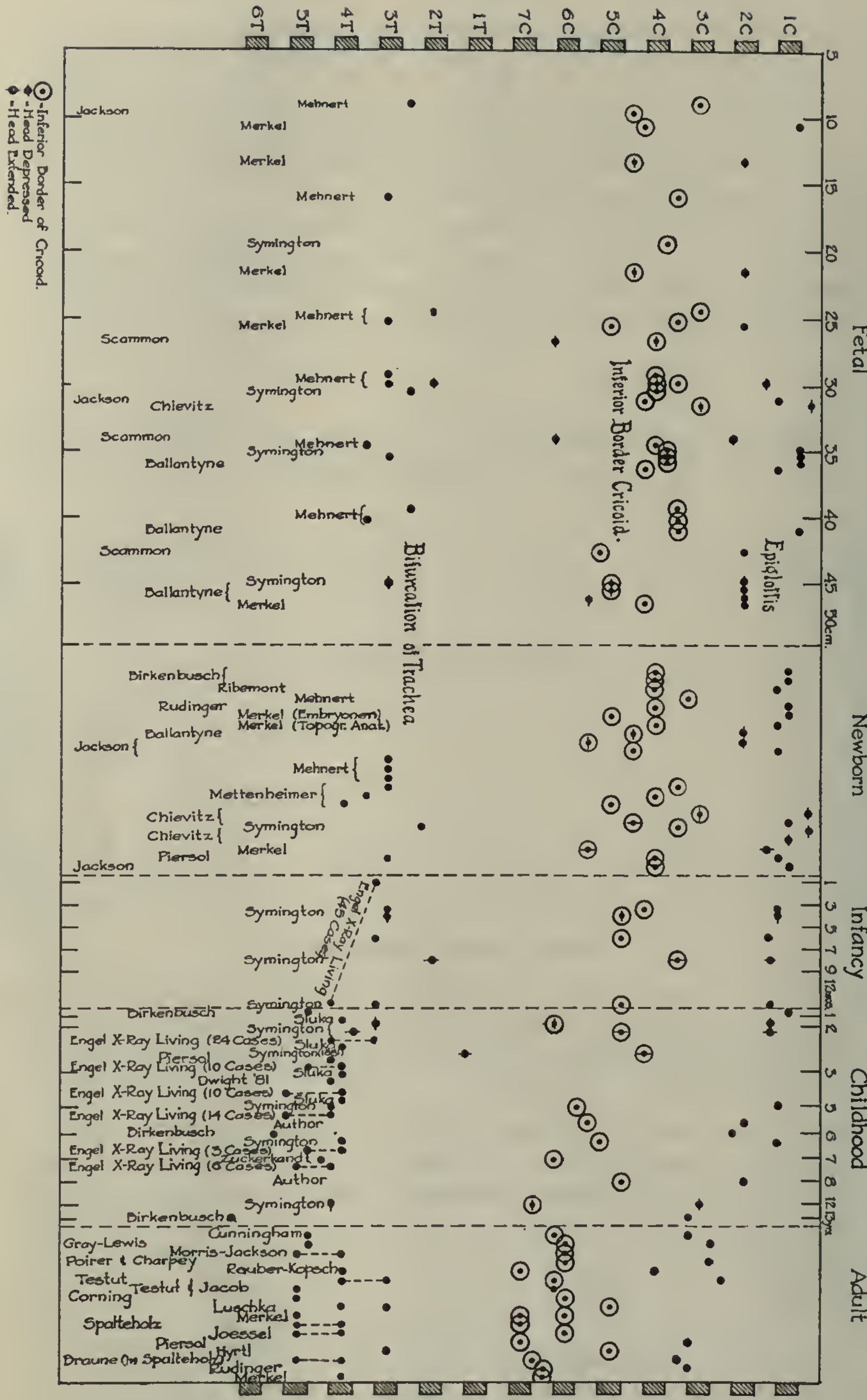

Chart 4.—The vertebral levels of the epiglottis, inferior margin of the cricoid cartilage and the tracheal bifurcation for prenatal and postnatal life as recorded in the literature.

about 2 years, another descent is apparent; and by the thirteenth year, the bifurcation has dropped a distance of one vertebra and disk to the level of the fourth and fifth thoracic vertebrae. This limit is apparently maintained during adult life.

Cameron (1922),[31] in a study of the abdominal viscera in fetal life, concludes that, of these organs, only the cecum, splenic flexure and sigmoid flexure undergo a descent in regard to the vertebral column, and Solhaug (1923)[32] finds that the bladder, uterus and ovaries of the pelvic organs descend caudalward.

In order to determine the descent of the lungs from early fetal life to the period of the new-born and in postnatal life, the uppermost and lowermost extent of these organs were noted in relation to the vertebral column and the data in the literature were surveyed. The relation of the upper poles of the lungs to the suprasternal notch was also noted. The data for the right lung are plotted in Chart 2.

The relation of the upper limit of the right lung to the sternal notch is a practically constant one during fetal life. It is found in the majority of cases to be at the same level as the notch, though there are some which extend above it, the greatest distance in these being 9 mm.

On plotting the upper limit of the right lung against the vertebral column, there seems to be a slight caudal shifting. The range is from the upper border of the seventh cervical to the inferior border of the second thoracic vertebra. The upper limit of the right lung makes a descent after the 20 cm. crown-heel length from between the seventh cervical and the first thoracic to between the first and second thoracic vertebra in the new-born, a descent of about one vertebra and disk.

The lower limit of the right lung in relation to the vertebral column shows a definite descent. In the 10-15 cm. group, the range is between the upper border of the ninth and the lower border of the tenth thoracic vertebra. From the 25 cm. length to the end of the series, the drop is distinct, as is indicated by the fact that the inferior margin of the lungs descends as low as the inferior margin of the twelfth thoracic vertebra in the full-term new-born child. The descent approximates a distance measured by one vertebra and intervertebral disk.

The relation of the left lung to the sternal notch and to the vertebral column is shown in Chart 3. The relation to the sternal notch is quite similar to that of the right lung. The majority are level with the notch though there are a number which extend several millimeters above and a few that are very slightly below it.

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[31] Cameron, A. L.: The Topography of the Abdominal Viscera in the Late Embryonic and the Fetal Period of Man as Determined by Graphic Reconstruction, abstr., Anat. Rec. **23**:12, 1922.

[32] Solhaug, S. B.: A Study of the Developmental Topography of the Pelvic Organs of the Female Fetus, Thesis, Doctor of Philosophy, University of Minnesota, 1923.

The upper limit of the left lung (Chart 3) undergoes slight descent after the 20 cm. body length. Up to this length, the range is from the upper margin of the seventh cervical to the lower margin of the first thoracic vertebra. The drop from this point on to the condition as found in the new-born infant is of about one vertebra and disk, and the range extends from the upper margin of the first to the middle of the second thoracic vertebra at birth. The descent is slight, as was the case in the right lung, and it is probable that this descent is real, though it must be slight and does not occur until after the fetus has attained a length of about 20 cm. total body length, or beginning in the fifth fetal month.

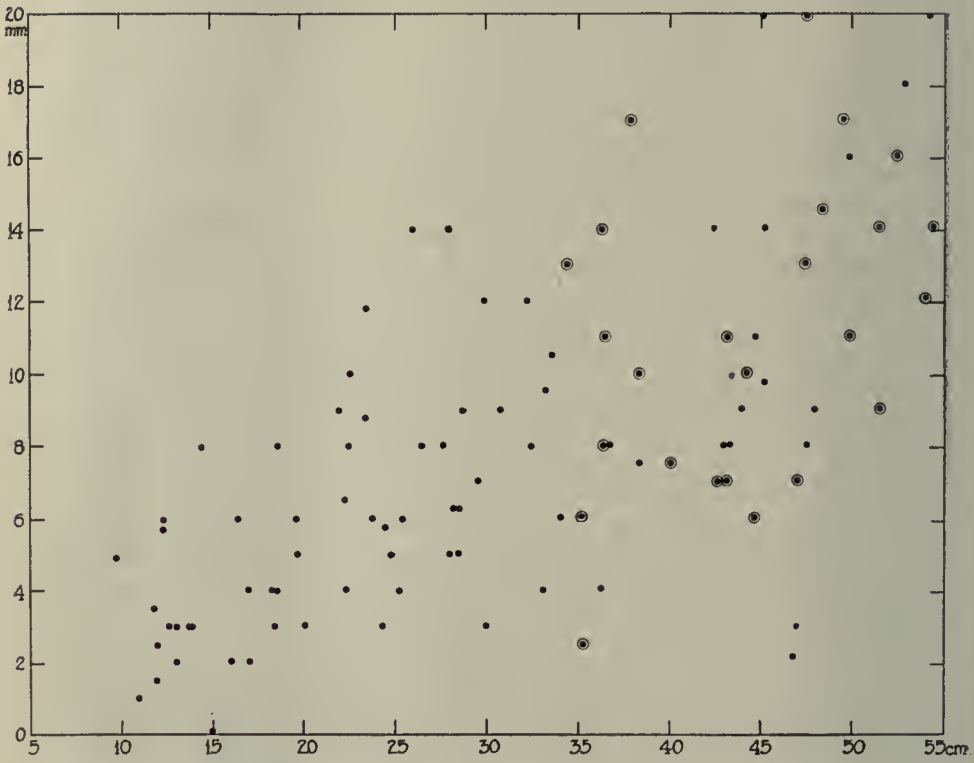

Chart 5.—Field graph of the depth of the cardiac notch plotted against total body length in the fetus and the new-born.

The inferior margin of the left lung (Chart 3), like that of the right lung, undergoes a definite descent. Up to a total body length of 20 cm., the range is from the upper margin of the ninth to the inferior margin of the tenth thoracic vertebra. From this point on, the descent is clearly indicated, and in the new-born group, the range has dropped to the levels between the middle of the tenth and the middle of the eleventh thoracic vertebra, a total drop of one vertebra and disk.

Considering both lungs, it may be concluded that the relation to the sternal notch is constant; that the upper limit of the lungs may descend slightly, and that the lower limit of the lungs, until the period of early infancy, undergoes a more definite descent of from one to two vertebrae in extent.

The vertebral levels of the adult (Chart 4) as given in the literature range as follows: The upper limit at the first thoracic vertebra and the lower limit opposite the ninth to the twelfth thoracic vertebrae. The adult vertebral levels of the lungs correspond quite closely to those found in the new-born infant. Therefore, any increase in length of the lungs in postnatal life must be accompanied by a corresponding increase in length of thorax.

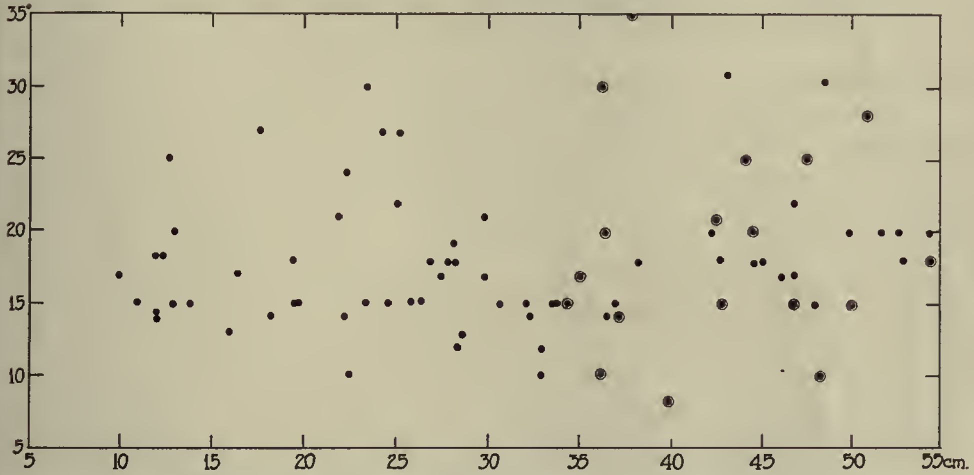

Chart 6.—Field graph of the angle of the right bronchus plotted against total body length in the fetus and the new-born.

(*b*) *The lobation of the lungs.*—Many observers have noted the variation in lobation of the lungs, notably Henle[33] who not only described them but diagrammed several of them. More recently, Spandolini,[34] in a comprehensive study of the morphology of the lungs, utilizing a series of 175 individuals, 125 adults and fifty fetuses of various stages of development, discusses lobation of the lungs.

My material consists of the lungs of a series of 101 fetuses and new-born children. It was found that the greater amount of variation occurs in the right lung, since thirty-seven, or 36.8 per cent., of the total 101 right lungs were typical in their lobation; whereas, sixty-four, or 63.3 per cent., were atypical. Variation from the normal lobation in the left lung is rather infrequent, as is indicated by the fact that but 5.8 per cent., or six out of the total of 101, were abnormal in their lobation, and ninety-five, or 94.2 per cent., were typical.

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[33] 33. Henle, J.: Handbuch der systematischen Anatomie des Menschen, Braunschweig, 1873, Ed. 2, Vol. 2, p. 274 and Figure 207.

[34] 34. Spandolini, I.: Contributo allo studio della morphologia del pulmone, Arch. ital. di Anat. e di Embryol. **2**:604, 1913.

The variation from the accepted normal of three lobes in the right lung and two lobes in the left lung may take form in either an increase in the number of fissures or a decrease due to their underdevelopment.

In the right lung, it was found that incomplete development of the fissures was the more frequent, with a total of sixty-one, or 60.3 per cent., of the cases showing this deficiency, and but three cases, or 2.9 per cent., presenting accessory or supernumerary fissures. The incompleteness of fissures varies greatly in extent, there being several cases of special note. One right lung had a total absence of the horizontal fissure, and the oblique fissure did not reach the base of the lung. Another modification of the fissuration of especial interest is one which was present in four of the right lungs. Here it was found that the horizontal fissure was not complete in that it failed to reach the median border of the lung, and that the oblique fissure, instead of being quite straight in its course, had, at the level of the incomplete horizontal fissure, a pyramidal tonguelike process which projected medially and inferiorly into the underdeveloped horizontal fissure. The presence of supernumerary fissures in the right lung is not frequent, there being but three cases, or 2.9 per cent., of the total number. Of these three cases there were two in which the extra fissure extended laterally from the oblique fissure at the level of the horizontal fissure to such an extent that one might say that these lungs were composed of four lobes.

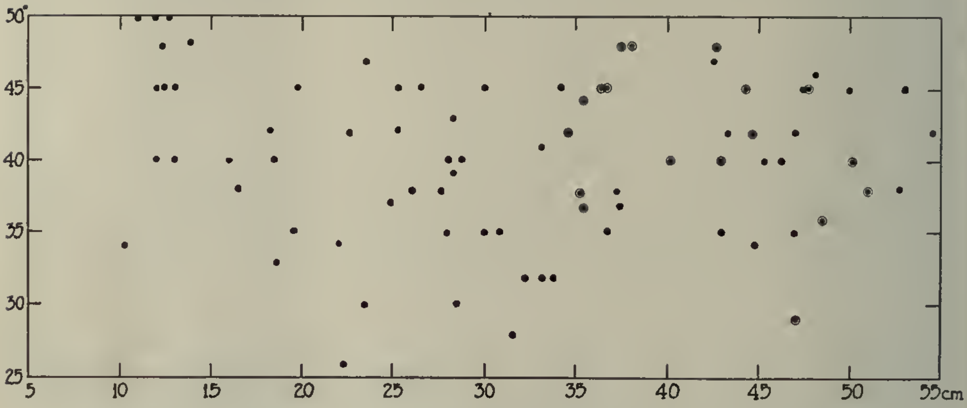

Chart 7.—Field graph of the angle of the left bronchus plotted against total body length in the fetus and the new-born.

In the left lung, abnormal fissuration is relatively infrequent, there being but six of the total of 101 left lungs with abnormal lobation. Of these, three, or 2.9 per cent., of the total had incomplete fissures, and three, or 2.9 per cent., were lungs in which there were supernumerary fissures. The latter were incomplete horizontal fissures which tended to divide the lung into three lobes similar to those normally found in the right lung.

Spandolini,[34] in his series of fifty fetuses and new-born children, found that only 49.1 per cent. of the right lungs were normal in the oblique fissure and but 36.7 per cent. of the horizontal fissures were complete. He found that the fissures in the left lung were normal in but 66 per cent. of the cases. His findings in the left lung are much higher than those in my series, in which the normally fissured lungs totaled 95, or 94.2 per cent.

(*c*) *The angles of divergence of the bronchi.*—The deviation of the right bronchus from the midsagittal plane (Chart 6) shows great variation in all of the groups of specimens. In the 10 to 15 cm. group, it ranges from 13.2 to 35.8 degrees, and in the new-born group, from 10 to 30 degrees. However, throughout fetal life, the greater number of cases are grouped between 14 and 22 degrees and the average may be taken as about 18 degrees.

The deviation of the left bronchus from the midsagittal plane, like that of the right bronchus, varies to a great extent, and the angle is much greater than is that of the right bronchus. The range (Chart 7) in the 10 to 15 cm. group is from 34 to 50 degrees and in the new-born infants from 38 to 45 degrees. The average angle for the left bronchus may be stated to be about 42 degrees.

(*d*) *The cardiac notch.*—The cardiac notch (Chart 5) shows a tendency to increase in size along with the increase in total body length, there being, however, very wide fluctuations in this measurement throughout the fetal period. The measurement in the 10 to 15 cm. group is from 1.0 to 6.0 mm., and, in the new-born group, ranges from 2.0 to 20.0 mm.

SUMMARY

1. The descent of the respiratory system in relation to the vertebral column during childhood is not peculiar to this period in the development of the individual. It is merely a stage in a process which is already manifested in early fetal life and which continues to operate through infancy, childhood and maturity.

2. The larynx. During fetal life, the topography of the epiglottis shows practically no change. It remains quite constantly opposite the first cervical vertebra. This level persists through infancy and child-

hood until puberty, when the adult relationship is attained, i. e., it lies opposite the third cervical vertebra.

The inferior margin of the cricoid cartilage, and therefore the lower limit of the larynx, descends during the course of prenatal life from opposite the third to opposite the fourth cervical vertebra, a distance represented by one vertebra and intervertebral disk. During infancy, this relationship remains constant; but during later childhood, another descent to the level of the sixth cervical vertebra takes place, a drop of two vertebrae and one disk. With the attainment of maturity, a further descent of one vertebrae and disk has occurred, so that the inferior limit of the larynx is then opposite the seventh cervical vertebra.

3. The bifurcation of the trachea. The tracheal bifurcation undergoes a descent caudalward in relation to the vertebral column during fetal life. It drops from opposite the third to opposite the fourth thoracic vertebra, a descent of one vertebra and disk. The natal relationship persists during infancy, but in childhood another descent takes place, and by puberty the bifurcation is opposite an area between the fourth and fifth thoracic vertebrae. This level is then maintained, apparently, through adult life.

4. Topography of the lungs. The apices of the lungs remain at practically the same level as the suprasternal notch throughout the course of fetal life.

The upper poles of the lungs in relation to the vertebral column undergo a slight descent during prenatal life from a level opposite the seventh cervical or first thoracic vertebra to the upper margin of the second thoracic vertebra, a distance of one vertebra or less. This level is apparently maintained throughout the course of postnatal life.

The inferior margins of the lungs during fetal life undergo a descent from between the ninth and tenth to opposite the tenth to twelfth thoracic vertebrae, a distance equivalent to slightly more than one vertebra and disk. The latter level, present at birth, coincides quite closely to the levels as given in the standard texts and atlases for the adult, thus indicating the probability that the postnatal growth in length of the lungs is closely correlated with the increase in length of the thorax.

5. The lobes of the left lung in the human fetus do not vary much from the condition in the adult, there being but 5.8 per cent. of the total with atypical lobation. The lobes of the right lung depart quite markedly from the conditions usually described in the adult, there being but 36.8 per cent. of the total with the typical three-lobed condition.

6. The depth of the cardiac notch. The extent of the cardiac notch during prenatal life is extremely variable in a group of cases of the same body length. There is, however, a general increase in depth with increase in total body length.

THE EFFECT OF INADEQUATE DIET ON THE INORGANIC SALT CONTENT OF MOTHER'S MILK *

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It is well recognized that the milk of the dairy animal has a marked tendency to remain constant in composition even under adverse conditions, changes in the diet, particularly in respect to the inorganic constituents, not readily affecting the concentration of the various components.

In a review of the subject of milk secretion as related to diet, E. B. Meigs [1] has given an exposition of the dietary factors influential in increasing or diminishing both the milk yield and the concentration of its various constituents, as brought out by the extensive experimental work which has been carried on with dairy and other animals. In brief, it has been found that in early lactation the cow has a remarkable power to secrete milk normal in yield and composition on inadequate rations, the shortage being supplied at the expense of its own body, as shown by loss of weight. In later stages of lactation, the total milk yield and frequently the concentration of protein and of fat can be considerably affected in a short time by changes in the organic components of the diet, most readily by decrease or increase in the amount of protein or of total nutrients in the rations. On the other hand, it may take weeks or months before the effect of the reduction of inorganic constituents in the diet can be seen in the milk.

Most of the experimental work with animals on changes in inorganic salt content of the diet in relation to milk composition have been concerned with sodium chlorid, calcium salts and phosphates. Many experiments with sodium chlorid have shown that neither additions of that salt to the diet in considerable amounts nor reductions in the intake, even to total deprivation, have any significant effect on its concentration in the milk.

Denis and Sisson [2] have made some interesting experiments concerning inorganic salt in milking goats. They found no change in the chlorin content of the milk of one animal after twenty-four days on

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* From the wards and Nutritional Research Laboratories of the Hospital for Sick Children and the subdepartment of pediatrics, University of Toronto.

1. Meigs, E. B.: Physiol. Rev. **2**:204 (April) 1922.

2. Denis, W., and Sisson, W. R.: J. Biol. Chem. **46**:483 (May) 1921.

a diet without sodium chlorid, and no increase after feeding the same animal relatively high doses of that salt for eleven days. Only when doses were given large enough to raise the chlorin content of the blood plasma 18 per cent. was there an increase in the chlorin concentration of the milk, and with this occurred a greatly diminished milk yield. Later,[3] they tried to increase the calcium concentration in the milk of goats by feeding large doses of calcium chlorid, but obtained negative results. The chlorin content of both blood and milk was increased in two of the animals, and in the blood only in a third. Intravenous injection of 1.87 gm. of calcium chlorid in a volume of 75 c.c. resulted in a large increase in both calcium and chlorin content of the blood and in the chlorin concentration of the milk, but there was no increase of the calcium of the milk, which was tested at intervals during the day.

Jordan, Hart and Patten[4] have shown that a reduction of phosphorus in the rations of cattle reduces the percentage of fat in the milk without affecting the total yield or the phosphorus content of the milk, and increasing the phosphorus intake results in an increased proportion of fat in the milk, but no increase of the phosphorus.

Several groups of investigators, notably Forbes and his collaborators[5] and Hart and his associates,[6] have brought out the striking fact that the milking cow or goat can have a negative calcium and phosphorus balance from an insufficient supply of these elements in the diet or of the vitamins that promote their assimilation or of both factors, and yet show normal calcium and phosphorus content of both blood and milk and little immediate diminution in the milk supply. This is to be attributed to the ability of these animals to take large amounts of calcium and phosphorus from their bones to supply the lack in their rations. Incidentally, the tables presented by Hart and others show, in the case of one goat with a small and rapidly diminishing milk supply, an abnormally high concentration of calcium and phosphorus in the milk.

Meigs[1] reports the experiments of Fingerling[7] in which he reduced the calcium and phosphorus intake of lactating goats, with at first no effect on the milk, but with immediate loss of these elements from the animals' bodies. After several weeks, the milk yield fell off and its calcium and phosphorus concentration rose, though the total amount of both minerals excreted in the milk was decreased. Return of the normal amount of calcium and phosphorus to the rations restored the milk to normal.

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[3] 3. Denis, W.; Sisson, W. R., and Aldrich, M.: J. Biol. Chem. **50**:315 (Feb.) 1922.

[4] 4. Jordan, W. H.; Hart, E. B., and Patten, A. J.: Am. J. Physiol. **16**:268, 1906.

[5] 5. Forbes, E. B., et al.: Bull. Ohio Agricultural Exper. Station, No. 295, 1916; No. 308, 1917; No. 330, 1918.

[6] 6. Hart, E. B.; McCollum, E. V., and Humphrey, G. C.: Am. J. Physiol. **24**:86, 1909. Hart, E. B.; Steenbock, H.; Hoppert, C. A., and Humphrey, G. C.: J. Biol. Chem. **53**:21 (July) 1922.

[7] 7. Fingerling, G.: Die landwirtsch. Vers.-Stat. **75**:1, 1911.

Meigs and Woodward [8] found evidence sufficient for them to conclude that the calcium and phosphorus content of the diet of the period preceding lactation is more important in the effect on the milk secretion than that during lactation and that the full effect of deficiencies in these elements may not become apparent for years.

In the investigation of the effect of diet on the salt content, much less work has been done on human milk than on the milk of lower animals. Analyses of human milk recorded in the literature [9] show considerable variation in concentration of most of the inorganic constituents; but as these values are not correlated with definite information concerning the diets of the mothers, the variation proves nothing for the question under discussion. An average of ten samples of late milk (at ten months or later) show a lower calcium, magnesium and phosphorus content and higher concentration of sodium and chlorin than the corresponding averages for mature milk (that secreted from the beginning of the second month to the tenth month), and these changes are regularly associated with a considerably reduced milk production. A table including these supposedly normal values will be presented later.

Bahrdt and Edelstein [10] found a lowered content of calcium in the milk of mothers of rachitic and anemic children, but they consider the number of their analyses too few to give much weight to the observation. They gave calcium to a mother but obtained no definite effect on the content of calcium in the milk. Bunge, as quoted by Freund,[11] found no significant effect on the chlorin content of the milk from giving a nursing mother a diet free from sodium chlorid, and later one containing 30 gm. of the salt in the day's food. Sisson and Denis,[12] who have recently made a study of the chlorin content of human milk, found wide variations in both directions in samples of milk from different individuals and in those from the same individual collected at different times. They conclude, however, that the milk of the normal mother giving regularly a normal supply, after the second week of lactation to the end of the sixth month, is most constant in chlorin content. They found no effect produced by ingestion of sodium chlorid, but they did not use excessive doses.

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[8] Meigs, E. B., and Woodward, T. E.: Bull. U. S. Dept. Agriculture, No. 945, 1921.

[9] Talbot, F. B.: A Summary of Present Knowledge of Human Milk, Am. J. Dis. Child. **7**:445 (June) 1914. Holt, L. E.; Courtney, A. M., and Fales, H. L.: A Chemical Study of Woman's Milk, Especially Its Inorganic Constituents, Am. J. Dis. Child. **10**:229 (Oct.) 1915.

[10] Bahrdt, H., and Edelstein, H.: Jahrb. Kinderh. **72**:16, 1910.

[11] Freund, W.: Jahrb. Kinderh. **48**:137, 1898.

[12] Sisson, W. R., and Denis, W.: Observations on Salt Content of Human Milk, J. A. M. A. **75**:601 (Aug. 28) 1920. Sission, W. R., and Denis, W.: Studies on Inorganic Constituents of Milk, Am. J. Dis. Child. **21**:389 (April) 1921.

Studies of the diets of mothers nursing rachitic infants, made by Hess and Unger,[13] and by Dunham, Willis and Guy, as quoted by E. A. Park[14] in his recent review of the subject of rickets, although no milk analyses are reported, suggest that, in at least some of the cases, the milk may have been abnormal in calcium or phosphorus content as well as in other respects. Hess and Unger found that the diets of these women were made up of meat, fish, rice, potatoes, cereal, tea and coffee, with little milk and what vegetables were included mostly canned. Dunham, Willis and Guy found that the majority of the diets which they investigated provided less than the caloric requirement of mother plus child and that they were almost entirely lacking in fresh fruit and vegetables. In certain cases, the diet was low in calcium content, and in some, in phosphorus. They found in some instances that the mother's milk was low in caloric value.

With human milk as with that of the lower animals, though the tendency may be to constancy in concentration of inorganic constituents, the probability is that changes may be brought about by long-continued deficient or ill-balanced diets.

Four more or less defective diets of nursing mothers have come under observation at the Hospital for Sick Children during the last fifteen months. The diets are reported as those used during the period of lactation. The details were necessarily obtained from the mothers themselves and some allowance must be made for individual judgment regarding quantities taken and for minor omissions. Making due allowance, however, for such errors, the defects in the diets are sufficiently evident.

The milk of each mother was obtained in quantity under conditions calculated to insure typical samples. The content of calcium, magnesium, total phosphorus, chlorin, sodium and potassium was determined according to standard gravimetric methods. Estimation was made also of the calcium and phosphorus content of the infants' serum. The caloric values of the protein, fat and carbohydrate components of the diets were calculated according to the estimates given in Locke's "Food Values." As reported, they represent, unless otherwise stated, approximately the daily intake. Hoobler,[15] in a study of the protein intake of nursing mothers, gives the caloric value and the proportion of protein in a series of diets which he used. The total calories of the diets ranged from about 2,000 to 4,000, mostly from 2,300 to 3,000. He states that the diets including 3,700 calories resulted in overfeeding and did not give as good results as those of a value of 3,000. He emphasizes the importance of the nutritive ratio of the diet. By this is meant the ratio of the number of calories provided by protein to the sum of those provided by fat and by carbohydrate. This ratio for his series of diets varied between 1 : 4 and 1 : 15, but he considers the optimum range to be from 1 : 4 to 1 : 6. For cattle on standard rations, the values range from 1 : 4.5 to 1 : 8.5. This study of Hoobler's provides a useful standard of comparison.

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[13] Hess, A. F., and Unger, L. J.: Diet of Negro Mother, J. A. M. A. **70**:900 (March 30) 1918.

[14] Park, E. A.: Physiol. Rev. **3**:106 (Jan.) 1923.

[15] Hoobler, B. R.: Protein Diet and Human Milk, Am. J. Dis. Child. **14**:105 (Aug.) 1917.

OBSERVATIONS IN FOUR CASES

Case 1.—The diet consisted of approximately 33 ounces (976 c.c.) of milk (taken partly in two cups of cocoa and one cup of tea and on the cereal), one egg, a small amount of cornmeal porridge, two slices of bread and butter, one serving of potato, one serving of carrots, cauliflower or peas several times during the week but not every day, two small servings of preserved fruit and two or three chocolates. Sugar was added only to the cocoa. No meat had been eaten for about two years, but meat gravy was sometimes taken.

The caloric value was 1,800; the nutritive ratio (approximate), 1 : 6.5. The chief defects were a too low nutritive value and lack of fruit and vegetables. The distribution of calories as fat, protein and carbohydrate in this diet is good and the quantity of milk, which provided a fair supply of minerals, might have been sufficient if the diet had been satisfactory in other respects.

The child, aged 7 months, weight 16 pounds (7,257 gm.), had been nursed from birth. She was admitted to the hospital because of having bad stools and convulsions. She showed slight craniotabes and had no teeth. The blood calcium content was 9.7 mg. per hundred cubic centimeters of serum. The blood phosphorus was not determined.

The milk secretion averaged 18 to 19 ounces (532 to 562 c.c.) a day. The analyses showed its concentration of calcium and magnesium to be lower than the normal average, of potassium and phosphorus, higher; while that of sodium and chlorin was nearly the normal. No values, however, were outside the extremes reported for supposedly normal milks.

Case 2.—This diet included about 13 ounces (385 c.c.) of milk (taken wholly in eight cups of tea and on porridge and pudding), three and one-half slices of bread with oleomargarin, one serving of oatmeal or cornmeal porridge, one of potato, one of turnips or carrots about once a week, about 8 ounces (236 c.c.) of vegetable soup once a week, one serving of thoroughly stewed lean meat, one small piece of bacon once a week, one serving of rice pudding twice a week and one of stewed fruit about once a week. Sugar was taken in tea and on porridge and pudding in moderate amounts.

The caloric value was slightly over 2,000; the nutritive ratio (approximate), 1 : 6. The chief defects were too low nutritive value to supply the need of mother plus child, too great a proportion of carbohydrate and too little of fat, the small supply of sources of fat-soluble vitamin, lack of fruit and vegetables and far too little milk to provide the mineral requirement.

The child, aged 12 months, weight 21 pounds and 14 ounces (9,912 gm.), had been nursed from birth, receiving in addition during the preceding five months a little bread or bread and cow's milk. He was admitted to the hospital suffering from tetany, having spasms of the hands and feet. He was well-nourished, but showed through roentgen-ray examination signs of acute rickets. The blood calcium content was 5.2 mg. per hundred cubic centimeters of serum, the phosphorus, 6.8.

The milk supply seemed to be abundant, though the child nursed irregularly. One day he took 39 ounces (1,153 c.c.). Analyses showed calcium and magnesium content less than the normal average for mature milk but only slightly less than that for late milk. The content of potassium and of phosphorus was higher than normal and that of sodium and of chlorin nearly normal. No values fell outside the extremes found in the case of normal milk.

Case 3.—This mother was nursing twins. The diet included from 8 to 10 ounces (236 to 296 c.c.) of milk (taken wholly in two or three cups of tea and one of cocoa and on pudding), one egg, about four slices of white or brown bread with butter, one pork chop or one serving of minced meat, one potato, one serving of pudding, from three to five soda wafers or other biscuit and occasionally a piece of cake. She took sugar in the tea and cocoa, and on the pudding. Her intake included also eight cups of a galactagogue extract of cotton seed, which on analysis showed a high nitrogen content that, if computed entirely as protein, would make the substance 65 per cent. protein. It contained also 2.5 per cent. of fat or other ether extractives, 1.75 per cent. calcium, computed as calcium oxid, and 20 per cent. of reducing substances after hydrolysis. Before hydrolysis, there was no reduction. The iodin test showed no starch present. There was less sweet taste than would be expected if 20 per cent. cane sugar were present. Giving the benefit of the doubt as to both protein and sugar content, 300 calories have been alloted to the galactagogue added to the diet.

The total calories were 2,300; the nutritive ratio (aproximate), 1:3.5 (assuming the galactagogue to be 65 per cent. protein). The chief defects were: total caloric intake too low for mother and two infants, low proportion of fat in any case and too high proportion of protein, if the galactagogue contained the maximum amount of protein, entire lack of fruit and of vegetables other than potato and an entirely inadequate supply of milk. The low mineral content of the regular diet was increased to some extent by the calcium contained in the galactagogue.

The children, aged 4 months, weights 13 pounds and 1 ounce (5,925 gm.), 13 pounds and 12 ounces (6,237 gm.), had been nursed from birth. They were admitted to the hospital because of a cough and fever. Both had marked craniotabes and secondary anemia, and there was roentgen-ray evidence of chronic or healing rickets. The smaller child was given a blood transfusion after admission. This child's blood had a calcium content of 9.2 mg. per hundred cubic centimeters of serum and a phosphorus content of 2.6. The blood calcium of the other child was 9.7 mg. per hundred cubic centimeters and the phosphorus, 4.6 mg.

The milk production was about 20 ounces (591.5 c.c.) a day. It was found to be much lower in calcium and magnesium content than normal milk. The content of potassium and of phosphorus was nearly normal, that of sodium rather high and of chlorin rather low. The values found for calcium and magnesium fell below the extremes reported for normal mature milk.

Case 4.—This diet was the most abnormal in the series. It consisted of one or two fried eggs, meat three times daily, usually beef, preferred fat, occasionally pork chops, about two slices of bread with no butter, two servings of potato and sauerkraut once a week.

The caloric value was 1,700; the nutritive ratio (approximate), 1:2.3. The chief defects were a too low nutritive value, too great proportion of protein and too little of carbohydrate, too much meat, entire lack of milk, butter, fruit and of vegetables other than potato and the weekly serving of sauerkraut. The supply of minerals and of vitamins must have been far below the requirement.

The child, aged 6 months, weight 13 pounds and 13 ounces (6,264 gm.), had been nursed from birth, but was receiving at the time four or five supplementary feedings a day of cow's milk. He was admitted to the hospital for treatment of a subcutaneous abscess. He showed marked evidences of rickets including those revealed by roentgen-ray examination. The calcium content of the blood serum was 9.2 mg. per hundred cubic centimeters; that of phosphorus, 2.8 mg.

The supply of milk was small and nursing was stopped entirely soon after his admission to the hospital. The milk analysis showed very low calcium and phosphorus concentration, rather low magnesium and normal potassium, and abnormally high sodium and chlorin concentrations. The value for calcium was lower than the extreme for normal milk, that for phosphorus barely within the limits; while those for sodium and chlorin were greater than the normal extremes.

Table 1.—*Salt Content of Milk and Calcium and Phosphorus of Infant's Blood*

	Milk Salts, Gm. per Hundred C.c.			
	Case 1	Case 2	Case 3	Case 4
Total salts	0.2343	0.2076	0.1823	0.1928
Calcium oxid	0.0363	0.0367	0.0290	0.0290
Magnesium oxid	0.0056	0.0067	0.0035	0.0074
Phosphorus pentoxid	0.0512	0.0541	0.0418	0.0258
Chlorin	0.0392	0.0379	0.0309	0.0475
Potassium oxid	0.0801	0.0723	0.0584	0.0618
Sodium oxid	0.0145	0.0161	0.0195	0.0284
	Contents Infant Serum, Mg. per Hundred C.c.			
Calcium	9.7	5.2	9.7-9.2 (Larger of twins) (Smaller of twins)	9.2
Phosphorus	...	6.8	4.6-2.6	2.8

Table 2.—*Salt Content of Normal Milk*

	Milk Salts, Gm. per Hundred C.c.					
	Average for 17* Samples of Mature Milk	Extreme Values for 17 Samples of Mature Milk	Average for 10* Samples of Late Milk	Average for 11† Samples of Mature Milk	Extreme Values for 11 Samples of Mature Milk	Average for 3† Samples of Late Milk
Total salts	0.2063	0.1590-0.2433	0.1978	0.1955	0.1790-0.2484	0.1512
Calcium oxid	0.0472	0.0295-0.0702	0.0390	0.0416	0.0328-0.0567	0.0290
Magnesium oxid	0.0081	0.0052-0.0106	0.0070	0.0082	0.0060-0.0116	0.0069
Phosphorus pentoxid	0.0345	0.0212-0.0514	0.0304	0.0409	0.0260-0 0585	0.0385
Chlorin	0.0355	0.0251-0.0444	0.0442	0.0340	0.0244-0.0468	0.0245
Potassium oxid	0.0574	0.0366-0.0714	0.0575	0.0632	0.0522-0.0848	0.0451
Sodium oxid	0.0153	0.0031-0.0250	0.0195	0.0189	0.0049 0.0258	0.0165

* From twenty-seven analyses of Holt, Courtney and Fales.
† Analyses of Abderhalden, Blauberg, Pelka, Soldner and E. Schloss.

Table 1 gives the values found for the various salts in the four samples of milk and also the calcium and phosphorus content of the blood serum of the infants. Table 2 gives the averages and the extreme values found for the inorganic constituents of normal milk, which have been used above for comparison.

It is significant that the two specimens of milk in which the irregularities in salt content were greater than those presenting the extreme values for corresponding salts of normal milk were those of the two mothers whose diets showed the most glaring defects. Milk was entirely lacking or provided in an almost negligible amount, and fruit was entirely lacking, as was practicably every vegetable but potato. In addition, the total supply of nutriment was undoubtedly below the requirement. One of the twins in the one case, as well as the child of the other mother just referred to, had an abnormally low phosphorus content of the blood serum, the typical rachitic finding.

Continued use of a deficient diet by the nursing mother may have serious effects on the child, especially in the later stages of lactation, when the mother's reserve has become depleted. Observations on the lower animals even suggest that, if the diet of the mother has been habitually below her own need in one or more constituents, her milk may be below standard even from the beginning of lactation.[16]

The determination of calcium and phosphorus in the serum in the two additional cases here described was made by Dr. Tisdall.

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[16] Two of the cases described have already been reported (Brown, Alan; Courtney, A. M.; Tisdall, F. F., and MacLachlan, I. F.: A Critical Study of Two Cases of Rickets Developing in Breast Fed Infants, Arch. Pediat. **39**:559 (Sept.) 1922.

THE ACIDITY OF THE GASTRIC CONTENTS OF INFANTS *

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The object of this paper is to consider the acidity of the gastric contents of infants under normal and pathologic conditions; the influence of the diet on the degree of acidity, and the practical significance of the gastric acidity in relation to infant feeding.

There are various means of determining the degree of gastric acidity and of expressing the results. The titration of the gastric contents, following a test meal, has been the method most used in the case of adults, and the results are usually expressed in terms of "total hydrochloric acid," "free hydrochloric acid" and "combined hydrochloric acid." The results thus obtained are valuable for comparative purposes and serve to indicate, in a general way, the capacity of the stomach to secrete acid under standard conditions. This method has not been generally applied to the study of the gastric secretion of infants, as it is more difficult of application and the results obtained do not give the information desired.

A method which is easily applied and which gives information of greater significance consists in the determination of the concentration of the hydrogen ions in the gastric contents at the height of digestion. It is the free hydrogen ions which are responsible for the characteristic properties of all acids. The effective "strength" of any acid solution may be expressed in terms of the number of grams of ionized hydrogen present in solution. A normal solution of hydrochloric acid contains approximately 1 gm. of ionized hydrogen per liter; a tenth normal solution, 0.1 gm. ionized hydrogen, and a millionth normal solution, 0.000001 gm. In order to simplify the expressions and to avoid the use of many ciphers, it is customary to use logarithmic terms with negative exponents and indicate a tenth normal solution of acid as having a hydrogen-ion concentration of 10^{-1}, a millionth normal solution as 10^{-6}, or more simply as p_H 1, p_H 6, etc.

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* Received for publication, Sept. 6, 1923.

* From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital.

* A preliminary report on this work was read before the American Pediatric Society, Washington, D. C., May 1, 1922. Marriott, W. McK.; Davidson, L. T., and Harshman, L. P.: Studies on the Digestion in Infancy, Proc. Am. Pediat. Soc. **34**:39-45, 1922.

As the action of hydrochloric acid in the processes of digestion is largely, if not entirely, due to the number of free hydrogen ions present, the determination of the hydrogen-ion concentration is of more significance than the determination of the total gastric secretion by titration methods. Various foods, especially milk, as will be seen later, have the property of binding large amounts of acid and converting the hydrogen into a nonionized form, thus to all intents and purposes neutralizing the acid. When foods of the type mentioned are given, much of the hydrochloric acid secreted is rendered inactive; hence, if one is to gain an idea of the effective acid concentration, it is necessary to determine the hydrogen-ion concentration at the height of digestion following a regular feeding. This method gives one a true idea of conditions actually present in the stomach at the time when the customary food is being digested. For practical purposes, this information is of more value than that obtained by titration methods applied to gastric contents obtained after other than customary feedings.

In our work, we have removed the gastric contents from infants at the height of digestion and have determined the hydrogen-ion concentration by means of the simple dialysis-indicator method,[1] which has been shown to yield results closely approximating those obtained by the electrometric method.

TECHNIC

Gastric contents were removed by means of a soft rubber catheter and a syringe. The catheter was introduced through the mouth or the nose. It was found that this could be done by an experienced person without causing much discomfort to the infant. Whenever violent retching, vomiting or the outpouring of large amounts of mucus occurred, the attempt to obtain gastric contents was abandoned until the following day, as otherwise the results were not reliable because the alkaline mucus partly neutralizes the acid present. Gastric contents were removed two hours after a feeding. It was found that the acidity of the chyme reached a maximum within one and a half hours after a feeding, and maintained this maximum acidity for about an hour. It was found that more uniform results were obtained on contents removed at the end of two hours than at any other period after the feeding. With one or two exceptions, all infants studied were on a four-hour feeding interval.

When the conditions mentioned were fulfilled, it was found that determinations made on the same infant on successive days were regularly in close agreement. Whenever possible, a number of determinations were made on each infant. In determining the hydrogen-ion concentration of the samples, small portions were first tested with indicators to obtain the approximate p_H. Three c.c. of the contents was then placed in a clean collodion sack and dialyzed against 3 c.c. of physiologic sodium chlorid solution for fifteen minutes. The collodion sack was then removed and 6 drops of appropriate indicator added to the dialysate, which was then compared with the standard buffer solution, containing indicator. Approximately correct readings were possible by comparison with the color chart in Clark's book, but this was checked in all cases by comparison with buffer standards made up according to the description of Clark. The indicators used were thymol blue (p_H 1.2-2.8), brom phenol blue (p_H 3.0-4.6), methyl red (p_H 4.6-6.0) and brom cresol purple (p_H 5.8-6.8).[2]

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[1] Levy, R. L.; Rowntree, L. G., and Marriott, W. McK.: A Simple Method for Determining Variations in the Hydrogen-Ion Concentration of the Blood, Arch. Int. Med. **16**:389 (Sept.) 1915.

THE GASTRIC ACIDITY OF NORMAL INFANTS FED ON BREAST MILK

The gastric contents of forty-one normal infants under 1 year of age were studied. Of these, twenty-three were fed at the breast and seventeen were receiving breast milk from the bottle. All were fed at four-hour intervals. The results obtained are plotted graphically in Chart 1, first column. Each dot represents the p_H of the gastric contents of an individual infant. When more than one determination was made, the results were averaged.

It will be seen from the chart that in over two-thirds of the gastric contents studied the p_H fell between 3 and 4. The average for the whole series was 3.75, this figure being in close agreement with that obtained by Davidsohn,[3] who, using the electrometric method, found an average p_H of 3.8 for a series of normal breast-fed infants. Other observers have obtained results, some of which varied considerably from the foregoing. These variations are to be explained by differences in the technic employed. A summary of previous results obtained is given by Davidsohn.[4]

THE GASTRIC ACIDITY OF ABNORMAL INFANTS FED ON BREAST MILK

In order to determine the effect of the infant's nutritional condition and the effect of the presence of infections on the acidity of the gastric contents, a group of sixteen infants was studied. These infants were all hospital patients, most of them extremely undernourished. These infants and others in the series were suffering from acute and chronic infections, including otitis media, pyelitis, pneumonia, osteomyelitis and bacillary dysentery. The ages of the infants varied from 3 weeks to 9 months. The majority were between 3 and 5 months of age. All were receiving breast milk in amounts customary for the age. The results obtained are plotted graphically in Chart 1, second column. It will be seen that the p_H of the gastric contents of most of these infants varied between 4.4 and 4.8. All had a p_H above 4. The average for the series was 4.74. As we are dealing with negative exponents, this result indicates that the actual concentration of hydrogen ions in the stomachs of these sick infants at the height of digestion averaged only one-tenth as much as that of normal infants receiving the same food. There was a definite deficiency in the gastric secretion. In a number of instances, it was possible to study the same infants, first while normal, and subsequently when suffering from an infection. There was regularly a marked decrease in gastric acidity in the presence of infection. The further significance of this lowered gastric acidity will be discussed subsequently.

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[2] For further details of the technic, the reader is referred to Clark, W. M.: The Determination of Hydrogen-Ions, Baltimore, Williams & Wilkins Co., 1920; and Levy, Rountree and Marriott: Footnote 1.

[3] Davidsohn, H.: Arch. f. Kinderh. **69**:239 (April) 1921.

[4] Davidsohn, H.: Arch. f. Kinderh. **69**:142 (April) 1921.

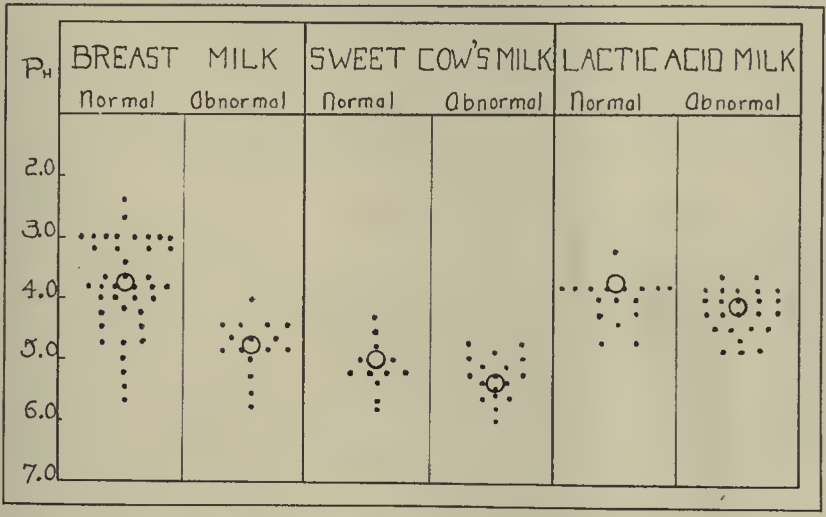

Chart 1.—Hydrogen-ion concentration of the gastric contents of infants. Each dot represents the average p_H for an individual infant. The circle represents the average for each group.

THE INFLUENCE OF THE CHARACTER OF THE FEEDING ON THE GASTRIC ACIDITY

When cow's milk is added to an acid, a portion of the hydrogen of the acid is converted into a nonionized form, and the true acidity of the solution is thus greatly reduced. This is due to the fact that cow's milk contains a large amount of "buffer" material; that is to say, substances capable of uniting with considerable amounts of acid or alkali without undergoing a great change in chemical reaction. In cow's milk, the chief buffer substances are the phosphates and the calcium caseinate. Of the total buffer substances present, approximately one-third exists in the whey and the remaining two-thirds in the curds. Human milk contains a smaller amount of buffer material, and, therefore, does not convert as much of the hydrogen of the acid into a nonionized form.

The effect of adding varying amounts of tenth normal hydrochloric acid to breast milk and to cow's milk are illustrated in Chart 2. On referring to the curves, it will be seen that, although cow's milk has an initial acidity slightly greater than that of breast milk, the addition of such an amount of hydrochloric acid as 30 c.c. of tenth normal acid to 100 c.c. of milk results in a relatively slight change in hydrogen-ion concentration (p_H 6.6-5.85) ; whereas, the addition of the same amount of acid to breast milk changes the hydrogen-ion concentration to a much greater extent (p_H 6.9-3.4). In order to bring cow's milk to a p_H of 3.4, over 100 c.c. of acid is necessary, or approximately three times as much as in the case of breast milk. Judging from these results, one would expect that, when cow's milk was fed to an infant, the hydrogen-ion concentration at the height of digestion would be less than when an equal amount of breast milk was fed. This was found to be the case.

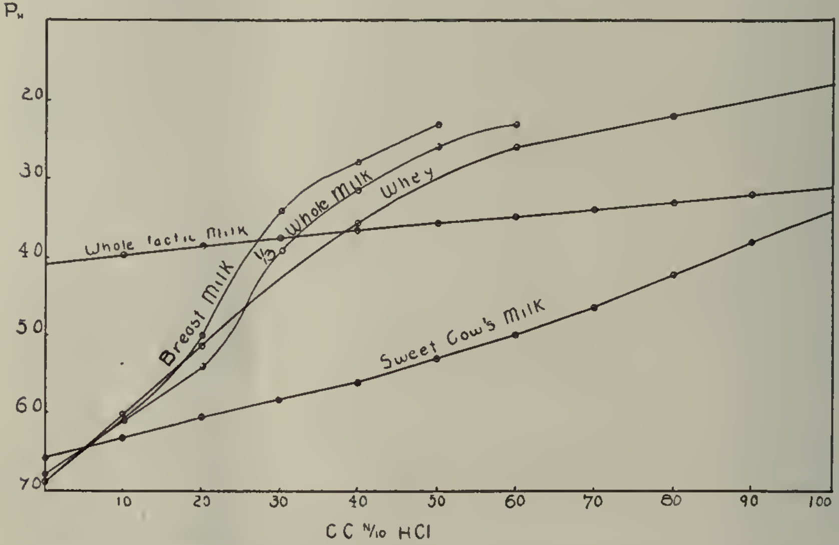

Chart 2.—Titration curves of breast milk, sweet cow's milk, lactic acid milk, diluted cow's milk and whey.

THE GASTRIC ACIDITY OF NORMAL INFANTS FED ON COW'S MILK

On feeding undiluted cow's milk to a group of the normal infants whose gastric acidity on breast milk feeding had been studied, it was found that the average p_H at the height of digestion was 5.3. This means an effective concentration of acid of less than one-twentieth that in the case of the breast-fed infants. To another group of normal infants accustomed to cow's milk, the average hydrogen-ion concentration following a meal of undiluted whole cow's milk was 4.75. From this, it would appear that infants fed on cow's milk gradually adapt the gastric secretion to this type of food in such a way that a greater amount of hydrochloric acid is secreted by the stomach, and this partially, though by no means completely, overcomes the effects of the buffer substance.

The results of the feeding of undiluted whole milk to normal infants are presented graphically in Chart 1, third column. The average for the whole series was 5.1. One infant studied was not included in this series because of the unusual character of the preceding feeding. This infant, 4 months old, had been fed on large amounts of undiluted cow's milk for three months. The gastric acidity in this case was p_H 3.3. This finding accords well with the assumption that the feeding of cow's milk ultimately results in a compensatory increase in gastric acidity.

THE GASTRIC ACIDITY OF ABNORMAL INFANTS FED ON COW'S MILK

In feeding undiluted cow's milk to malnourished infants and those suffering from acute infections, it was found that the gastric acidity at the height of digestion was less than in any other series of infants studied. Sixteen of the abnormal infants whose gastric contents on breast milk feeding had been determined were fed on undiluted whole milk. The average p_H at the height of digestion was 5.35. The results appear in graphic form in Chart 1, fourth column.

THE GASTRIC ACIDITY OF NORMAL INFANTS FED ON LACTIC ACID MILK

Lactic acid milk, containing from 0.5 to 0.7 per cent. of lactic acid, prepared by the action of lactic-acid-producing organisms, or by the addition of lactic acid to whole milk, has a considerable portion of its buffer substance neutralized by the lactic acid present. The titration curve of such milk with hydrochloric acid appears in Chart 2. From the chart, it will be seen that the addition of 30 c.c. of tenth normal hydrochloric acid to 100 c.c. of lactic acid milk leads to a hydrogen-ion concentration very close to that obtained when the same amount of hydrochloric acid is added to breast milk (p_H 3.6-3.8). As this is the average hydrogen-ion concentration of the gastric contents of normal infants fed on breast milk, one would expect that if lactic acid milk were fed in the same amounts to normal infants, the same hydrogen-ion concentration would be attained at the height of digestion.

Undiluted whole lactic acid milk was fed to seventeen normal infants, most of whom had already been studied with breast milk feeding. The average hydrogen-ion concentration was found to be 3.71, as compared with 3.75 in the case of breast milk. The results appear in graphic form in Chart 1, fifth column.

THE GASTRIC ACIDITY OF ABNORMAL INFANTS FED ON LACTIC ACID MILK

Referring again to the titration curve of whole lactic milk in Chart 2, it will be seen that the curve is a flat one, and that the hydrogen-ion concentration varies within narrow limits, even with considerable variations in the amount of acid added. This milk has a p_H approximating 4 before any acid at all is added. From these facts, one would expect that the feeding of lactic acid milk to abnormal infants with deficient gastric secretion would result in a fair degree of acidity of the gastric contents at the height of digestion, and this was found to be the case.

TABLE 1.—*Hydrogen-Ion Concentration (p_H) of Gastric Contents of Normal Infants and Those Suffering From Infections or Nutritional Disturbances, Fed on Breast Milk, Sweet Cow's Milk and Whole Lactic Acid Milk*

	Breast Milk	Cow's Milk	Acid Milk
Normal	3.75	5.1	3.71
Abnormal	4.74	5.35	4.1

Twenty-six infants suffering from severe malnutrition and infections were studied. Most of the infants in this group were previously studied to determine the effect of feeding breast milk. The results appear in graphic form in Chart 1, sixth column. The average p_H at the height of digestion was 4.1, or somewhat more acid than in the case of the same group of infants fed on breast milk. This figure closely approximates the p_H of the gastric contents of normal breast-fed infants.

A summary of the gastric findings in normal and abnormal infants fed on various types of foods appears in Table 1.

THE SIGNIFICANCE OF THE GASTRIC ACIDITY

The acid of the gastric contents when present in large enough amounts to lead to a sufficient concentration of hydrogen ions performs a number of functions.

A certain hydrogen-ion concentration is necessary in order for peptic digestion of protein to occur. It has been found that peptic digestion begins at p_H 4 and is optimum at p_H 2.[5] From the results which we have obtained, it is apparent that some peptic digestion was possible in over two thirds of the normal breast-fed infants examined and in a fair number of the infants fed on lactic acid milk. No peptic digestion was possible in the case of the infants suffering from nutritional disturbances or infections whether fed on breast milk or sweet cow's milk. It was possible, however, in a fair proportion of the sick infants fed on lactic acid milk. Even in the case of normal infants fed on sweet cow's milk, the hydrogen-ion concentration was insufficient for any peptic digestion.

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[5] Sørensen, S. P. L.: Biochem. Ztschr. **21**:131, 201; **22**:352, 1909.

It is difficult to estimate the importance of peptic digestion in infancy. Certainly, a considerable portion of the protein of the food passes the pylorus without having undergone any digestion, even under normal conditions, and it may be argued that all of the protein could escape peptic digestion without any disadvantage to the infant. On the other hand, it has been shown that the peptones resulting from peptic digestion are capable of stimulating the flow of pancreatic juice and bile,[6] and even the small amount of peptone formed might very well function in this way.

A rennin action on casein occurs at a lesser degree of gastric acidity than does peptic digestion. Casein is well coagulated by rennin at p_H 5.[5] With a lesser degree of acidity, the passage of unchanged casein past the pylorus is favored. The recent observations of Schloss and Anderson[7] on the passage of unchanged protein through the intestinal wall of athreptic infants suggests that denaturization of the casein by rennin coagulation may be of importance in preventing such absorption. The acidity of the gastric contents is known to regulate in some measure the pyloric reflex and gastric motility. Cowie and Lyon[8] have demonstrated that either an excess or a deficiency of acid leads to a prolonged emptying time of the stomach. Our own observations have been that, in general, a larger portion of the feeding was present, and could be removed by a catheter at the end of two hours, in the case of infants with a deficiency in gastric acidity than in those with an acidity approximating that of normal breast-fed infants. We do not believe, however, that the degree of acidity is the only factor influencing the gastric motility in such infants.

An important function of the acid of the gastric juice is its antiseptic action. It has been shown that, at p_H 5, marked inhibition of the growth of members of the colon, dysentery and typhoid group of bacilli occurs, and that at p_H 4 complete inhibition or death of the

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6. Flieg, C.: Arch. Internat. d. Physiol. **1**:286, 1904.
7. Schloss, O. M., and Anderson, A. F.: Proc. Am. Pediat. Soc., 1923.
8. Cowie, D. M., and Lyon, W.: Am. J. Dis. Child. **2**:252, 1911.

organisms takes place.[9] It appears probable from the work of Bessau and Bossert[10] that invasion of the duodenum with members of the colon group of bacteria is a contributory factor in the production of diarrhea and nutritional disturbances of infants. A sufficient degree of acidity of the gastric contents such as occurs in normal breast-fed infants or in infants fed on lactic acid milk greatly decreases the chance of infection of the upper intestine with potentially harmful bacteria.

A further function of the acid in the gastro-intestinal tract is a stimulation of the flow of pancreatic juice, bile and intestinal secretions. This fact is noted when the acid chyme pours into the duodenum and is, according to Bayless and Starling, due to the production in the intestinal mucosa of the hormone "secretin." As acids other than hydrochloric acid have the same affect in stimulating the flow of these digestive juices,[6] it is evidently the hydrogen ion which is the active agent. Such being the case, a sufficient degree of acidity of the gastric contents must be an important factor in favoring subsequent intestinal digestion.

It was found by Klotz[11] that the addition of moderate amounts of lactic acid to the food of infants results in distinctly better absorption of all food elements from the gastro-intestinal tract. In these experiments, the amount of acid most favorable in its affect was just about sufficient to neutralize the buffer substances to such an extent as to lead to a normal gastric acidity.

From the foregoing considerations, it is evident that the acidity of the gastric contents may play an important rôle in the general processes of digestion and in the nutrition of infants. The experimental results recorded in the first part of this paper show that marked variations in gastric acidity occur and that, in general, a decrease in acidity is likely to be associated with nutritional and gastro-intestinal disturbances.

MEANS OF ALTERING THE GASTRIC ACIDITY OF INFANTS

The acidity of the gastric contents of an infant at the height of digestion may be low as the result of insufficient secretion of acid or as the result of administration of food of such high buffer value that the acid secreted is neutralized. When the gastric secretion is deficient, it may be the result of disease or malnutrition. In such instances, treatment directed toward the underlying condition usually results in an improvement in secretion. We have, however, at present no effective specific means of increasing the gastric secretion.

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[9] Shohl, A. T., and Janney, J. H.: J. Urol. **1**:211 (April) 1917. Ohta, K.: Jahrb. Kinderh. **85**:358, 1917.

[10] Bessau and Bossert: Jahrb. f. Kinderh. **89**:213, 1919.

[11] Klotz: Jahrb. f. Kinderh. **70**:1, 1909.

The acidity of the gastric contents at the height of digestion may be increased to a considerable extent by proper choice of food as regards buffer value. Breast milk has a low buffer value and can be fed in larger amounts than cow's milk. The feeding of diluted cow's milk is equivalent to feeding of a lesser total amount of milk, and there is, consequently, less neutralization of gastric acid. The feeding of cow's milk in 1 : 3 dilution leads to approximately the same concentration of acid at the height of digestion as when the same amount of breast milk is fed. The acid titration curve of 1 : 3 cow's milk is plotted in Chart 2, and from this it will be seen that such diluted milk reacts with acid in about the same manner as does breast milk. In the customary modifications of cow's milk for infant feeding the milk is diluted and the buffer substance thus proportionately reduced. These mixtures, and also whey (Chart 2) lead to fairly normal conditions of acidity in the gastric contents, but, unfortunately, do not supply sufficient food value as measured by calories. The additions made to such mixtures are usually carbohydrates, or cream, the former having no buffer value and the latter very little. Another means of reducing the buffer value of milk is by drying. In this process, a portion of the calcium and phosphate is converted to insoluble tribasic calcium phosphate, and to this extent the buffer substances are reduced.

Another method of eliminating the buffer substances of milk is to saturate the buffer with acid. This is equivalent to augmenting the acid of the gastric juice. Hydrochloric acid would appear to be the natural acid to add, and certainly, as far as conditions in the gastrointestinal tract are concerned, it would be ideal. Unfortunately, however, only limited amounts of hydrochloric acid can safely be added to the food of an infant because of the fact that this acid is not destroyed in the body, but must be eliminated; and this throws a rather severe strain on the acid-base regulating mechanism and may lead to acidosis. Faber [12] has recommended the use of a small amount of hydrochloric acid, not sufficient to saturate the buffer, and even this amount has been shown by him to render the cow's milk more suitable as a food for infants.

Organic acids are not open to the same objections as is hydrochloric acid, since these acids can be completely oxidized in the body. Lactic acid serves very well to neutralize the buffer of cow's milk. It is, furthermore, in reasonable amounts, free from any harmful effects. Acetic, citric and butyric acids tend to cause diarrhea. Certain other organic acids, such as oxalic, are definitely toxic, and others, although possibly suitable from the physiologic standpoint, are difficult to obtain.

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[12] Faber, H. K.: Proc. Am. Pediat. Soc., 1923.

Everything considered, lactic acid is the acid of choice. It is an interesting coincidence that the amount of lactic acid ordinarily found in buttermilk, or lactic acid milk, is just sufficient to saturate the buffer substances of milk to such an extent that the additional acid required to bring the hydrogen-ion concentration to the normal average of gastric contents (p_H 3.8) is exactly the same as in the case of breast milk (Chart 2).

It has been known for many years that infants could usually tolerate larger amounts of sour than of sweet cow's milk, and it seems probable from the foregoing considerations that this increased tolerance is largely the result of the attainment of optimum conditions of acidity in the gastro-intestinal tract. In our experience, as good results are obtained on feeding sterile cow's milk acidified by the addition of lactic acid (from 0.5 to 0.7 per cent.). Such milk may be fed undiluted to even young babies without leading to the nutritional or digestive disturbances that so commonly occur when whole sweet cow's milk is fed undiluted. This method of rendering milk digestible possesses a distinct advantage over the dilution method in that considerably more milk, and consequently a larger amount of food, may be administered.

Table 2.—*Comparative Effects of Feeding Infants on Sweet Cow's Milk, Bulgarian Milk and Milk Acidified by the Addition of Lactic Acid*

		Bulgarian Milk			Acid Milk			Sweet Milk		
Case	Age	Days Fed	Total Gain, Gm.	Daily Gain, Gm.	Days Fed	Total Gain, Gm.	Daily Gain, Gm.	Days Fed	Total Gain, Gm.	Daily Gain, Gm.
1	5 days	10	360	36	14	540	38	12	250	21
2	2 weeks	30	900	30	17	600	35	14	200	11
3	2 weeks	16	600	37	14	800	57	7	220	30
4	4 weeks	21	600	28	14	580	41	5	120	24
5	4 weeks	14	560	40	12	560	47	16	410	25
6	8 weeks	12	400	33	14	450	32	14	150	11
7	8 weeks	28	900	32	7	250	36	8	150	20
8	10 weeks	7	350	50	17	850	50	16	550	34
9	10 weeks	12	500	42	18	500	28	8	0	0
10	16 weeks	14	400	21	17	600	35	9	0	0
Average				35			40			16

The favorable effect on the nutrition of acidification of cow's milk is well shown in a series of feeding experiments which we have carried out. Ten young infants in the wards of the hospital were fed for varying lengths of time on each of three diets; whole sweet milk, bacterially soured whole milk and whole milk acidified by the addition of 0.6 per cent. lactic acid. Sugar in the form of corn syrup was added to the milk in every instance. Each infant received the same amount of milk and of sugar during each period. The order in which the feedings were alternated was varied in the case of different infants. There were no digestive disturbances in any of the infants whether fed on bulgarian milk or on acidified milk. In a number of instances, however, diarrhea or vomiting occurred while the infants were taking the sweet milk. These symptoms disappeared on the resumption of acid milk feedings.

The results are summarized in Table 2.

It will be seen that the gain in weight was distinctly greater during the periods of feeding of one of the lactic-acid-containing milks, than during the sweet-milk periods. These observations have been amply confirmed in the case of several hundred infants in the hospital and clinic who have been fed on lactic acid milk for long periods of time. There has been regularly a more striking gain in weight and a lesser incidence of gastro-intestinal disturbances among this group of infants than among those fed on sweet-milk formulas. A more detailed discussion of the use of whole lactic acid milk appears elsewhere.[13]

We have rarely observed an excessive secretion of gastric acid in infancy, and we have seen no symptoms that could be attributed to excessive acidity of the gastric contents. It is possible, however, that some infants may suffer from hyperchlorhydria. In such infants, food with a high buffer value would be theoretically indicated.

SUMMARY AND CONCLUSIONS

1. The acidity of the gastric contents of a group of normal breast-fed infants at the height of digestion averaged p_H 3.75.

2. The acid normally present is sufficient to perform a number of important functions. Any considerable decrease in the amount of acid is likely to be associated with digestive disturbances.

3. The acidity of the gastric contents of infants suffering from infections or nutritional disturbances is distinctly lower than that of normal infants.

4. Sweet cow's milk, by reason of its high "buffer" value, is capable of neutralizing a considerable portion of the acid of the gastric juice. This is one important reason why large amounts of sweet cow's milk cannot be well tolerated by infants.

5. Milk containing from 0.5 to 0.7 per cent. of lactic acid does not neutralize the acid of the gastric juice to any greater extent than does breast milk. When such milk is fed undiluted to infants, the acidity of the gastric contents approximates that of normal breast-fed infants. It is probable that, for this reason, infants are able to tolerate large amounts of lactic acid milk.

6. In selecting a food for young infants, it is important to take into consideration the "buffer" or acid-binding qualities.

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[13] Marriott, W. M., and Davidson, L. T.: J. A. M. A., to be published.

PHYSIOLOGY OF EXERCISE

PART 3. AN INVESTIGATION OF CARDIOVASCULAR TESTS IN NORMAL CHILDREN AND IN CHILDREN WITH TUBERCULOSIS AND VALVULAR HEART DISEASE *

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In an investigation of the physical efficiency of schoolchildren, over a period of three years, we were impressed by (1) the high percentage of physically defective children; (2) the admission to school of physically subefficient children; (3) the inadequacy of the present system of physical examinations for the recognition and classification of abnormal conditions, and (4) the great need of objective methods for determining physical efficiency; the medical profession must admit that a mere anatomic basis for classification of disease is inadequate for this purpose.

Methods to determine physical efficiency are necessarily subjective, objective, or both. The subjective method concerns itself with an accurate history of the reaction of a person to his daily activities. Regarding objective methods, the literature in clinical medicine may be divided into two groups: (1) the quantitative measurement of capacity for physical work and (2) the reaction of the circulatory system to changes in posture and to measured amounts of work. This paper will limit itself to the discussion of the second group.

For a better understanding of the physiologic principles upon which cardiovascular tests are based, the meaning of the terms "functional capacity" and "reserve of the heart" may be clarified by the following theoretical example.

In a child, 11 years of age, weighing 35 kg., there are about 2.1 liters of blood. Forty-five seconds is required for a complete circulation of this amount of blood. With a systolic blood pressure of, let us say, 100 mm. (the pressure of a column of blood of 1.35 meters $= \frac{(100 \times 13.5)}{1{,}000}$), the work of the left ventricle in one minute would equal $1.35 \times 2.1 \times 4/3 = 3.78$ kg.; in one day, therefore, 5,443 kg. It has been estimated that the right ventricle accomplishes about one third the amount of the work done by the left ventricle. Thus, at rest, the total output of the heart in twenty-four hours would be about 7,257 kg., as compared with about 14,000 kg. performed by the heart of the adult. Since, in violent exertion, the pulse rate can increase two times, and in times of emergency, the systolic blood pressure can rise

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about 50 per cent., the cardiac output may increase two and a half times. This increase, amounting to 5.67 kg. in emergency, represents the reserve of the heart. In severe exercise, the total output or the functional capacity of the heart for each minute would equal $3.71 \times 5/2 = 9.45$ kg.

The nearest approach to an accurate, quantitative measurement of the total output of the heart has been made in the laboratory, by Krogh,[1] in his studies of the minute volume and the circulation time; by Pearce,[2] in his attempt to establish a cardiorespiratory index, and by others who have measured the quantity of blood from the blood vessels directly. Such methods obviously cannot be applied in every day clinical medicine.

The other so-called cardiovascular tests (Herz,[3] Selig,[4] Katzenstein,[5] Gräupner,[6] Barringer,[7] Crampton,[8] Schneider[9]) are not functional capacity tests, but are merely records of either the effect of change of posture on the pulse rate and the blood pressure or the effect of exercise on the circulatory reactions or both.

EFFECT OF CHANGE OF POSTURE ON THE PULSE RATE AND THE BLOOD PRESSURE

Pulse Rate.—In 1833, Donnell[10] observed that the pulse rate was slower in the lying posture than in the standing. Gräupner claimed to have found that the normal difference in the pulse rate from the standing to the lying posture, from seven to fifteen beats per minute, is considerably lessened or altogether lost in valvular heart disease. Geigel[11] believed that a variation of the pulse rate above thirty beats indicated a weakened heart condition. Kahn[12] claimed the average difference of the pulse rate to be sixteen beats for normal hearts. The majority of clinicians accept twenty beats as the limit of normal variation.

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[1] Krogh, A.: J. Physiol. **47**:112, 1913.

[2] Pearce, R. G.: Cardiorespiratory Mechanism in Health and Disease, Arch. Int. Med. **29**:139 (Feb.) 1921.

[3] Herz: Lehrbuch der Heilgymnastik, Wien, 1904, Deutsch. med. Wchnschr. **31**:215, 1905.

[4] Selig: Prag. med. Wchnschr. **30**:418; **31**:432, 1905.

[5] Katzenstein: Deutsch. med. Wchnschr. **30**:807, 1904; **41**:457, 1915.

[6] Gräupner: Die Messung der Herzkraft, München, 1905.

[7] Barringer, T. B., Jr.: Cardiac Function, Arch. Int. Med. **17**:363 (March), 670 (May) 1916; Heart's Functional Capacity, ibid. **20**:829 (Dec.) 1917; Tachycardia of Unknown Origin, ibid. **22**:805 (Dec.) 1918.

[8] Crampton: New York M. J. **93**:916, 1913.

[9] Schneider, E. C.: Cardiovascular Rating as Measure of Physical Fatigue and Efficiency, J. A. M. A. **74**:1507 (May 29) 1920.

[10] Donnell, cited by Barton, W. M.: Manual of Vital Function-Testing Methods and Their Interpretation, Boston, Richard G. Badger, 1917.

[11] Geigel, R.: Deutsch. Arch. klin. Med. **99**:634, 1910.

[12] Kahn, M. H.: M. Clinics N. America **2**:427 (Sept.) 1918.

Blood Pressure.—All authors agree that recumbency decreases the pulse rate. The opinion varies, however, regarding the effect of change of posture on the blood pressure, owing, probably, to differences in technic and to the sensitiveness of the blood pressure mechanism. A difference in the size of the cuff produces a difference in the reading. Readings taken at different levels of the meniscus differ. The blood pressure is different at different times of the day in the same position, different before and after meals. Psychic influences cause a change in blood pressure as great as from 10 to 20 mm. (e. g., entrance of the school principal into the room increased the blood pressure from 10 to 15 mm.). The first reading is practically always higher than the successive readings. The systolic blood pressure in children is so elastic and so sensitive to artificial changes that it is practically impossible to apply with sufficient accuracy what seems to be normal standards to diseased conditions.

Some authorities find the blood pressure in the lying posture from 10 to 15 mm. higher than that in the standing; others find the pressure standing from 10 to 15 mm. higher than that taken lying. All, however, are agreed that a difference exists between the two in normal conditions.

Crampton's test based on the effect of change of posture on the pulse rate and the blood pressure is most commonly used in this country.

Crampton correlates the differences of blood pressure and pulse rate resulting from a change in posture. He did not base his correlations on a mathematical analysis of physiologic data, but arbitrarily assumed that a correlation exists. He believes that a rise in blood pressure with a change in posture is an index of physical efficiency. He states: "This test will not reveal more than it assumes to test, i. e., the efficiency of the vasomotor system. It will not show the presence of a mitral lesion. Nor will it test other factors of efficiency such as will power, inhibition or skill. It does provide a means of making a definite record of an all important function."

Crampton emphasizes the necessity for considering both factors, the blood pressure as well as the pulse rate. His scale therefore consists of two parts: (*a*) the increase of the heart rate, 0 to forty-five beats, subdivided in groups of five beats each, on changing from the reclining position to the erect, and (*b*) the increase of the blood pressure of 10 mm. above and below zero on change of posture; e. g., if in a subject the heart rate increases twenty-one beats and the blood pressure 4 mm. when changing from lying to standing, the subject is rated 60. The 100 mark indicates a perfectly efficient working of the vasomotor system; the lower the mark, the less the physical fitness.

This test, so easy of application, would be a great aid in the functional diagnosis of heart disease provided it was scientifically criticism proof. We, therefore, undertook an investigation of (1) normal children,[13] (2) children with tuberculosis and (3) children with heart disease. We compared the results obtained in normal children with those in children suffering from disease. We furthermore determined statistically the correlation of the changes in the blood pressure and the pulse rate following a change of posture.

In applying Crampton's test, it was necessary to change Part 2 in the scale; that is, the differences in the blood pressure in the lying and standing postures, because our blood pressure readings in the lying posture were almost invariably higher than in the erect (800 determinations on 300 children were made). Our limit of normal variation of the differences of the blood pressure was 0 to 20 mm. Crampton's scale for the pulse rates was retained. The test was applied to sixteen normal children, sixteen tuberculous children and sixteen with heart affections, including one who suffered from heart block. This number was considered sufficiently large to form a basis for conclusions. The average rating for the normal children was 68.2, with a maximum of 87 and a minimum of 25; that for the tuberculous children was 58, with a maximum of 90 and a minimum of 20; and the rating for the children afflicted with heart disease was 68, with a maximum of 102.5 (diagnosis: mitral regurgitation, first degree) and a minimum of 40 (diagnosis: mitral regurgitation, hypertrophy of the heart, second degree). If Crampton's original scale is applied without a change in the blood pressure figures, the rating would be as follows: The average for normal children equals 32.6 (maximum, 63; minimum, 3); the average for tuberculous children equals 42 (maximum, 65; minimum, 20), and the average for children with heart disease equals 33 (maximum, 62.5, in a case of mitral regurgitation, hypertrophy of the heart, second degree; and minimum, 15, in a child with mitral regurgitation. Table 1 shows in detail that Crampton's scale, whether modified or not, cannot be used in children for the functional diagnosis of such diseases as tuberculosis and heart disease.

In addition, the correlation of the differences in the blood pressure and the pulse rate in the lying and standing postures was calculated. Six hundred readings of the pulse rate and the blood pressure were taken on 102 normal children ranging from 6 to 15 years of age.

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[13] Seham, Max, and Egerer-Seham, Grete: Physiology of Exercise in Childhood. Part 1. A Study of Normal Children of School Age, Am. J. Dis. Child. **25**:1-45 (Jan.) 1923.

Table 1.—*Findings in Sixteen Cases*

	Normal				Tuberculosis				Heart Disease				
Case	Pulse Rate St.-Ly.	Blood Pressure St.-Ly.	Crampton	Seham	Pulse Rate St.-Ly.	Blood Pressure St.-Ly.	Crampton	Seham	Pulse Rate St.-Ly.	Blood Pressure St.-Ly.	Crampton	Seham	Diagnosis
1	+ 5	—11	45	72.5	— 2	— 8	55	70	+12	—14	30	75	Pulmonary stenosis
2	+10	—13	35	72.5	+ 4	— 7	62.5	67.5	+22	—26	15	70	Mitral regurgitation
3	+23	— 5	63	37.5	+14	—16	20	75	+ 4	—14	40	85	Mitral regurgitation; stenosis
4	+13	—12	20	65	+12	— 9	42.5	62.5	+17	—10	30	55	Mitral regurgitation; hypertrophy
5	+10	—13	32	72.5	+ 1	— 4	65	60	+ 9	—12	35	70	Mitral regurgitation
6	+ 8	—12	40	75	+ 9	— 8	45	60	+27	— 5	32.5	32.5	Unclassified
7	+19	—20	7.5	80	+26	0	45	20	+10	— 7	47.5	57.5	Congenital heart disease, first degree
8	+18	— 1	52.5	32.5	+12	— 6	50	35	+ 9	—11	37.5	67.5	Mitral regurgitation, stenosis, second degree
9	+26	—17	2.5	62.5	+21	—12	20	55	+13	— 9	37.5	57.5	Mitral regurgitation, first degree
10	+ 6	—12	40	75	+ 7	—18	25	90	+18	— 8	35	50	Mitral regurgitation, second degree
11	+21	0	55	25	+20	—11	37.5	57.5	+ 9.5	—10	40	65	Mitral regurgitation, first degree
12	+15	—11	32	62.5	+ 2	— 4	65	60+	12	—13	32.5	72.5	Possibly compensated mitral regurgitation
13	+12	—19	20	87.5	+11	—17	32.5	82.5	+ 7	—20	20	95	Mitral and aortic lesion
14	+13	—12	30	65	— 1	— 6	60	65	+ 1	—21	22.5	102.5	Mitral regurgitation, first degree
15	+ 8	0	37	45	—18	—13	22.5	62.5	+17	— 4	4.5	40	Mitral regurgitation, hypertrophy, second degree
16	+20	—11	27	57.5	+18	0	55	30	+ 7	— 3	62.5	57.5	Mitral regurgitation, hypertrophy, second degree
Average			34.4	67.3	....	....	45.3	59.5	...	...	31 1	65.7	

TABLE 2.—*Pulse Rate and Blood Pressure of One Hundred and Two Normal Children*

Case	Age, Years	Pulse Rate			Blood Pressure			
		Variation St.-Ly.	X*	X^2	Variation Ly.-St.	Y†	Y^2	XY‡
1	15	15	+4	16	19	+8	64	+32
2	15	12	+1	1	15	+4	16	+4
3	15	19	+8	64	20	+9	81	+72
4	15	21	+10	100	20	+9	81	+90
5	15	10	+1	1	7	−4	16	−4
6	14	11	0	0	21	+10	100	0
7	14	16	+5	25	13	+2	4	+10
8	14	22	+11	121	5	−6	36	−66
9	14	26	+15	225	12	+1	1	+15
10	14	8	−3	9	7	−4	16	+12
11	14	1	−10	100	19	+8	64	−80
12	14	15	+4	16	6	−5	25	−20
13	14	10	−1	1	13	+2	4	−2
14	14	10	−1	1	8	−3	9	+3
15	14	9	−2	4	13	+2	4	−2
16	14	8	−3	9	17	+6	36	−18
17	14	15	+4	16	14	+3	9	+12
18	14	12	+1	1	11	0	0	0
19	14	6	−5	25	22	+11	121	−55
20	14	7	−4	16	12	+1	1	−4
21	14	10	−1	1	4	−7	49	+7
22	13	19	+8	64	1	−10	100	−80
23	13	20	+9	81	18	+7	49	+63
24	13	8	−3	9	5	−6	36	+18
25	13	17	+6	36	11	0	0	0
26	13	26	+15	225	17	+6	36	+90
27	13	13	+2	4	9	−2	4	−4
28	13	6	−5	25	6	−5	25	+25
29	13	10	−1	1	11	0	0	0
30	13	13	+2	4	5	−6	36	−12
31	13	3	−8	64	20	+9	81	−72
32	13	4	−7	49	11	0	0	0
33	13	16	+5	25	11	0	0	0
34	13	10	−1	1	4	−7	49	+7
35	13	10	−1	1	7	−4	16	+4
36	13	−2	−13	169	7	−4	16	+52
37	13	6	−5	25	12	+1	1	−5
38	12	14	−4	16	19	+8	64	−32
39	12	19	+8	64	12	+1	1	+8
40	12	3	−8	64	17	+6	36	−48
41	12	15	+4	16	16	+5	25	+20
42	12	8	−3	9	8	−3	9	+9
43	12	13	+2	4	4	−7	49	−14
44	12	4	−7	49	15	+4	16	−28
45	12	9	−2	4	13	+2	4	−4
46	12	8	−3	9	19	+8	64	−24
47	12	18	+7	49	20	+11	1212	+77
48	12	9	−2	4	4	−7	49	+14
49	12	18	+7	49	2	−9	81	−63
50	11	19	+8	64	4	−7	49	−56
51	11	12	+1	1	19	+8	64	+8
52	11	13	+2	4	11	0	0	0
53	11	14	+3	9	14	+3	9	+9
54	11	30	+19	361	8	+3	9	−57
55	11	6	−5	25	18	+7	49	−35
56	11	4	−7	49	12	+1	1	−7
57	11	4	−7	49	15	+4	16	−28
58	11	16	+5	25	10	−1	1	−5
59	11	9	−2	4	9	−2	4	−4
60	10	26	+14	196	6	−5	25	−70
61	10	10	−1	1	9	−2	4	−4
62	10	20	+9	81	8	−3	9	+81
63	10	20	+9	81	19	+8	64	72
64	10	8	−3	9	13	+2	4	−6
65	10	18	+7	49	17	+6	36	−42
66	10	10	−1	1	10	−1	1	+1
67	10	6	−5	25	8	−3	9	−15
68	10	−1	−12	144	14	+3	9	−36
69	9	29	+18	324	11	0	0	0
70	9	18	17	49	13	+2	4	+14
71	9	11	0	0	9	−2	4	0
72	9	8	−3	9	9	0	0	0
73	9	1	−10	100	9	−2	4	+20
74	9	11	0	0	11	0	0	0
75	9	9	−2	4	7	−4	16	+8
76	9	16	+5	25	6	−5	25	−25
77	9	6	−5	25	15	−4	16	+20
78	9	12	+1	1	13	+2	4	+2

TABLE 2.—*Pulse Rate and Blood Pressure of One Hundred and Two Normal Children—(Continued)*

		Pulse Rate			Blood Pressure			
Case	Age, Years	Variation St.-Ly.	X*	X^2	Variation Ly.-St.	Y†	Y^2	XY‡
79	8	14	+ 3	9	10	− 1	1	− 3
80	8	15	+ 4	16	12	+ 1	1	+ 4
81	8	12	+ 1	1	7	− 4	16	− 4
82	8	4	− 7	49	8	− 3	9	+21
83	8	14	+ 3	9	8	− 3	9	− 9
84	8	7	− 4	16	12	+ 1	1	− 4
85	8	12	+ 1	1	15	+ 4	16	+ 4
86	8	25	+14	196	13	+ 2	4	+28
87	8	−2	−13	169	9	− 2	4	+26
88	8	−1	−12	144	11	0	0	0
89	7	5	− 6	36	10	− 1	1	+ 6
90	7	7	− 4	16	8	− 3	9	+12
91	7	11	0	0	7	− 4	16	0
92	7	12	+ 1	1	9	− 2	4	− 2
93	7	15	+ 4	16	15	+ 4	16	+16
94	7	4	− 7	49	11	0	0	0
95	7	7	− 4	16	14	+ 3	9	−12
96	7	9	− 2	4	4	− 7	49	+14
97	7	4	− 7	49	15	+ 4	16	−28
98	7	8	− 3	9	9	− 2	4	+ 6
99	6	2	− 9	81	10	− 1	1.	+10
100	6	11	0	0	7	− 4	16	0
101	6	−1	−12	144	14	+ 3	9	−36
102	6	9	− 2	4	5	− 6	36	+12

* X, deviation of the differences of the pulse rates (standing minus lying).
† Y, deviation of the difference in systolic blood pressure (lying minus standing).
‡ XY, product of the paired differences of each case.

Standard deviation of pulse rate (from exact mean) $= \frac{X^2}{N} = 6.733$

Probable error of pulse rate $= \pm 4.541$

Standard deviation of systolic blood pressure (from exact mean) $= \frac{Y^2}{N} = 5.037$

Probable error of blood pressure $= \pm 3.402$

Coefficient of correlation $= \frac{XY}{N \times Y} = 0.04242.$

N, number of cases (102).

Table 2 presents the statistical calculation of these data. A study of this table shows definitely that the correlation between the differences of the pulse rate and the blood pressure on change of posture is negative (0.04242).

EFFECT OF CHANGE OF POSITION ON THE PULSE RATE AND THE SYSTOLIC BLOOD PRESSURE IN TUBERCULOUS CHILDREN AND CHILDREN WITH HEART DISEASE

Some observers claim that, in certain diseased conditions, the vasomotor tone is so reduced as to allow a state of "blood ptosis." This theory has been advanced as an explanation for supposedly abnormal changes of the blood pressure and the pulse rate on change of posture in chronic fatigue and in miscellaneous disease.

We studied the effect of posture on the pulse rate and the blood pressure in fifty children with tuberculosis and sixty-eight children with heart disease. The technic used was that described in Part 1 [13] of this series. The results are tabulated in Table 3. The figures in column Pulse Rate represent the differences between the pulse rates in the standing posture and the pulse rates in the lying, those in column Blood Pressure represent the differences in the systolic blood pressure in the lying position and that in the standing.

TABLE 3.—*Effect of Change of Position on the Pulse Rate and the Systolic Blood Pressure (6-15 Years)*

	Normal		Tuberculosis		Heart Disease	
Age, Years	Pulse Rate	Blood Pressure, Mm.	Pulse Rate	Blood Pressure, Mm.	Pulse Rate	Blood Pressure, Mm.
15	15.4	14.7	4.0	7.0	8.5	11.5
14	10.0	12.3	14.0	16.0	14.2	10.2
13	11.2	9.7	9.8	5.1	10.0	10.5
12	11.6	12.2	15.0	11.5	8.7	11.5
11	12.7	11.8	10.5	17.0	17.5	12.3
10	13.0	11.6	10.0	7.8	6.5	12.2
9	12.1	10.3	....	10.0	4.0	10.0
8	9.2	10.3	10.5	9.0	12.5	11.5
7	9.2	10.2	....	....	....	12.0
6	10.0	9.0	....	....	13.5	10.0

It can be seen at a glance that there is little difference in the effect of change of posture on the circulatory reactions in different conditions. This is more clearly brought out in Table 4, which contains the averages, maximal, and minimal, of the differences of the pulse rates and of the blood pressures, respectively, for all ages. A change of posture (from lying to standing) increases the pulse rate 11.4 beats and reduces the blood pressure 11.2 mm. in normal children; 10.5 beats and 10.4 mm. in tuberculous children; 9.3 beats and 11.2 mm. in children with heart disease.

The average ratio of pulse rate standing: pulse rate lying, and the average ratio of blood pressure lying: blood pressure standing is practically the same in the above mentioned conditions.

TABLE 4.—*Average, Moximal and Minimal Findings in Normal, Tuberculous and Heart Conditions*

	Pulse Rate			Blood Pressure		
Condition	Averages for All Ages	Maximum	Minimum	Averages for All Ages	Maximum	Minimum
Normal	11.4	15.4	9.2	11.2	14.7	9.0
Tuberculosis	10.5	15.0	4.0	10.4	17.0	5.1
Heart disease	9.3	14.2	4.0	11.2	12.3	10.0

Schneider's Test.—Schneider's cardiovascular test is based upon changes in the circulatory reactions on change in posture and after exercise.

Schneider arbitrarily established a "scoring scheme" comprising six factors: (*a*) the heart rate while the subject is lying down; (*b*) the heart rate while the subject is standing; (*c*) the increase in the number of beats in the pulse rate when the standing and reclining postures are compared; (*d*) the acceleration in the pulse rate after exercise; (*e*) the time taken by the pulse to return to normal, and (*f*) the rise or fall in the systolic blood pressure on standing. The scores for each of the six items range from + 3 to — 3. A perfect score is 18. For detailed information, the reader is referred to Schneider's article.[9] Schneider claims that his scoring scheme "recognizes that fatigue or derangement may be evidenced" in each of the six factors enumerated above. Schneider examined fifty-four aviators who were pronounced ailing and physically below normal by medical officers. Of these fifty-four subjects, only six had a score of 10 or better, while 88.8 per cent. had scores ranging between 9 and — 1. These figures, according to Schneider, seem to indicate that a score of 9 or less is "characteristic" of physically unfit men.

In another group of 150 patients, forty-six scored 9 or less. Medical examiners recorded abnormal conditions in thirty of the forty-six; that is, in 65.2 per cent. of the cases. In these subjects, Schneider's cardiovascular data ran parallel with the medical diagnosis.

In our study of normal children, tuberculous children and those suffering from heart disease, we necessarily had to modify Schneider's scale, because his observations were carried out on adults. Since the pulse rates vary with the age in childhood, we arranged a scale for the pulse rates starting with the lowest figure and ending with the highest found for each year. We then divided the differences into six groups according to Schneider. Sections B, D and E in Schneider's scale hold good for children of school age. We changed only the type of exercise, allowing the children to do ten full dumbbell swings (420 foot pounds). In section F, Schneider allots 3 points for a rise of 8 mm. or more in the blood pressure from the reclining posture to the standing, and — 1 point to a fall of 6 mm. or more. As mentioned before, in our series, no rise but almost invariably a fall of the blood pressure was observed. Therefore, all of our subjects would have to be rated in section F (— 1) if we apply the test literally.

Normal children: Three children, 12 years of age, and two children, 11 years of age, all in perfect physical condition, were rated according to Schneider's modified scale.

The three 12-year-old children scored + 1, — 1 and + 4 points, respectively. One child, 11 years old, received 5 points, the second, of the same age, 4 points; while, on repetition of the experiment, the latter received 0.

Because no data were available for the maximum rise and reaction time in tuberculous children and those afflicted with heart disease, we thought it advisable to compare just the four sections (A, B, C, and F).

On the basis of a perfect score of 12 points, the normal children, 12 years of age, received 0, 2 and 3 points, respectively, and the 11-year-old normal children were rated 0 and 3 points.

In three tuberculous children (aged 12 years), the rating was 5, 5 and 3, respectively, which is higher than in the normal children of the same age.

Three children (12 years old) with heart disease had the following scores: Case 1 (diagnosis: mitral regurgitation, vertical heart) 6 points; Case 2 (diagnosis: mitral regurgitation, myocarditis chronic, second degree) — 2 points; Case 3 (diagnosis: mitral regurgitation, first degree) 3 points. We thus have a case of heart disease receiving a rating of six points, while a perfectly normal child rated 0. In general, children with tuberculosis and heart disease rated higher than normal children.

Barringer's Test.—In 1898, Gräupner first determined the effect of exercise on the pulse rate and the blood pressure in normal adults and in adults with valvular heart disease. He made the following observations:

1. An abrupt drop of the blood pressure after severe muscular exertion or a slight rise (10 mm.) followed by a quick fall to a level below the preexercise level is evidence of functional insufficiency of the heart.

2. If the blood pressure remains high after cessation of work, and then suddenly falls, it indicates fatigue of the heart muscle.

3. If the blood pressure after work is lower than before exercise and then slowly ascends to normal, it is also a sign of myocardial insufficiency.

In 1916, Barringer confirmed most of Gräupner's conclusions. In addition, he established another sign of so-called myocardial insufficiency: "the delayed rise." He found, in normal adults and later in subjects with heart disease, that, after sufficiently severe exertion, the maximum reading of the systolic blood pressure occurs at sixty seconds or later rather than shortly after exercise (within thirty seconds). This "delayed rise" he considered indicative of myocardial insufficiency in normal subjects as well as in heart disease. Wilson[14] confirmed Barringer's work in children.

In Part 1 of this series, the circulatory reactions in normal children after exhaustive exercise were published. It was then stated that the maximum reading was obtained on an average at twenty-four seconds after cessation of work, only one delayed rise being obtained. The discrepancy between Barringer's and our results may lie in the fact that we took our readings within from five to ten seconds after cessation of work and at periods of from five to ten seconds thereafter. Again, we did not feel justified in considering as secondary rises that were less than 3 mm. higher than the next highest reading, because changes in the blood pressure of 3 mm. lie within the limit of error. In Part 2 of this series, the circulatory reactions in collapse following exhaustive exercise were reported.[15] The curves of the pulse rate and the blood pressure show almost invariably an abrupt drop immediately after exercise, the first reading being as a rule the highest.

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[14] Wilson, M. G.: Circulatory Reactions to Graduated Exercise in Normal Children, Am. J. Dis. Child. **20**:188 (Sept.) 1920.

Table 5.—*Effect of Measured Amounts of Work Upon the Pulse Rate and the Blood Pressure (Thirty-Five Full Length Dumbbell Swings)*

Normal							Heart Disease						
	Blood Pressure				Pulse Rate			Blood Pressure				Pulse Rate	
			Percentage of Recovery at		Percentage of Recovery at					Percentage of Recovery at		Percentage of Recovery at	
Age, Years	Maximum Rise, Mm.	Time Max. Reading, Sec.	120 Sec.	180 Sec.	120 Sec.	180 Sec.	Age, Years	Maximum Rise, Mm.	Time Max. Reading, Sec.	120 Sec.	180 Sec.	120 Sec.	180 Sec.
14......	39	45	79.1	86.6	100	100	15......	47	15	84.3	94.1	100	100
14......	35	30	88.6	93.5	100	100	14......	30	35	82.8	86.5	81.9	90
13......	35	55	76.3	86.9	...	87.5	14......	24	40	100	100	100	100
13......	46	55	77.3	86.8	100	100	14......	28	40	95	96.2	100	100
13......	35	45	79.0	82.8	100	100	13......	33	30	86.5	95.7	...	92
13......	40	35	94.5	100	100	100	13......	47	40	83.6	93.1	91	91
12......	35	25	85.4	90.8	87.5	91.8	13......	41	40	81.7	89.2	79.2	91.6
12......	37	35	86.6	94.2	85.7	90	12......	27	30	81.7	86.8	...	100
12......	35	35	86.5	87.2	...	80	12......	65	10	81.5	82.6	100	100
11......	32	30	87.9	96.3	...	100	12......	30	20	95.8	95.8	83.4	83.4
10......	19	35	87.8	93.1	100	100	12......	49	65	73.3	82.1	100	100
10......	43	35	71.6	93.0	100	100	10......	30	20	95.4	100.0	100	100
9......	37	25	86.9	96.3	...	...	8......	41	20	87.9	92.3	80	88.9
Average	41	39.4	83.4	91.3	97	95.5	Average	37.8	31.1	85.3	91.9	91.0	95.1

EFFECTS OF MEASURED AMOUNTS OF WORK ON THE PULSE RATE AND THE BLOOD PRESSURE

The opinion seems to prevail that in normal persons the circulatory reactions after exercise differ from those in subjects afflicted with heart disease, although equal amounts of work were performed.

To confirm or to refute this supposition, children between the ages of 8 and 15 years were studied. The first group consisted of thirteen normal children between the ages of 9 and 14; the second group of an equal number of children with heart disease, ranging between the ages of 8 and 15.

The exercise given consisted of thirty-five full length swings with two 4-pound dumbbells (only one child, 8 years old, swung a pair of 2-pound dumbbells). The technic described in Part 1 [13] was employed. The following items are tabulated in Table 5: (1) the maximum rise and the time of maximum reading of the blood pressure (Columns 1 and 2); (2) the percentage recovery of the blood pressure at 120 seconds and 180 seconds, respectively (Column 3), and (3) the percentage recovery of the pulse rate after the same period of time (Column 4).

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[15] Seham, Max, and Egerer-Seham, Grete: Physiology of Exercise in Childhood. Part 2. Study of Collapse in Normal Children, Am. J. Dis. Child. **26**:254 (Sept.) 1923.

Comparing the results obtained in normal children with those obtained in children having heart disease, one is impressed by their similarity. The maximum rise of the blood pressure in children with heart disease is about 3 mm. lower than that in normal children. This certainly lies within the limit of error for blood pressure readings. The time of maximum reading is slightly lower in heart disease, 31.1 seconds as against 39.4 seconds in normals. The percentage recovery of the blood pressure amounts to 83.4 and 91.3, respectively, in normal children, and 85.3 and 91.9, respectively, for those with heart disease. The only difference lies in the percentage recovery of the pulse rate at 120 seconds, that for normal children being 97, as against 91.0 for children with diseased hearts. This difference, however, cannot be considered sufficient to be of practical value in diagnosing myocardial sufficiency.

Table 6.—*Effect of Maximum Dumbbell Exercise on the Blood Pressure*

	Rise, Mm.			Time of Reading, Seconds			Percentage of Recovery at 180 Seconds
	Average	Maximum	Minimum	Average	Maximum	Minimum	
Normal cases (50 subjects, ages 9 to 15)............	47.5	105	10	39.9	53	20	86.8
Tuberculosis (30 subjects, ages 9 to 15)............	33.6	49	21	38.5	75*	20	86.2
Heart disease (30 subjects, ages 8 to 15)............	38.4	55	16	36.3	85†	15	89.0

* One delayed rise

† Two delayed rises in the same subject.

EFFECT OF MAXIMUM DUMBBELL EXERCISE ON THE SYSTOLIC BLOOD PRESSURE

Fifty normal children, thirty tuberculous children and thirty children with pathologic heart conditions were studied as to the effect of maximum work on the circulatory reactions by means of full length dumbbell exercise.[13] Table 6 shows that the maximum rise of the blood pressure was highest in normal children (45.7 mm.), probably owing to the larger quantity of work performed. In those having tuberculosis or heart disease, the maximum reading was 33.6 mm. and 38.5 mm., respectively. It is interesting to note that, in spite of the varying quantities of work performed by each individual group, the average time of the maximum reading of the blood pressure was practically the same (39.9, 38.5 and 36.3 seconds, respectively).

CONCLUSIONS

1. The so-called cardiovascular tests, in use today, do not measure the functional capacity of the heart.

2. Crampton's, Schneider's and Barringer's tests do not seem to be of value in the diagnosis of physical fitness or cardiovascular ability in tuberculosis and heart disease in children.

3. Delayed rises did not occur after exhaustive exercise, either in normal children or in those with tuberculosis or heart disease.

RÉSUMÉ OF THE LITERATURE ON SKIN DISEASES OF INFANTS AND CHILDREN (1920-1923) *

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The contributions to medical literature on the skin diseases of infants and children have been numerous the past three years. Those of real value or marking advance in our knowledge, however, have been few. It has been my purpose to include only these in this review. In some instances, it has seemed profitable to review articles published before the year 1920.

ECZEMA

The most interesting advancement in the skin diseases of infants and children has been the demonstration of the relationship of protein sensitization to eczema, one of the most common skin diseases of children.

Using the scratch method of applying the proteins, O'Keefe[1] found that 41 per cent. of the cases of eczema in bottle-fed infants and older children whom he tested gave a positive reaction to proteins. In forty-one cases of breast-fed infants with eczema, 61 per cent. gave positive cutaneous reactions.

In Schloss'[2] series of seventy-seven cases of eczema in infancy and childhood, 65 per cent. gave a positive reaction to the cutaneous protein test.

Sidlick and Knowles,[3] Engman and Wander[4] give similar proportions of reactions in infants and children with eczema, while Spohn[5] gives a higher percentage of positive reactions in a smaller number of children studied.

Shannon,[6] in 1921, demonstrated that egg protein passed through the mother's milk and could sensitize the nursing infant of mothers

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* From the Department of Pediatrics and Infectious Diseases, University Hospital, Dr. D. M. Cowie, director.

[1] O'Keefe, E. S.: Boston M. & S. J. **183**:569 (Nov. 11) 1920; **185**:194 (Aug. 18) 1921.

[2] Schloss, O. M.: Allergy in Infants and Children, Am. J. Dis. Child. **19**:433 (June) 1920.

[3] Sidlick, D. M., and Knowles, F. C.: Value of Cutaneous Sensitization Tests Employed in Eczema and Papular Urticaria of Childhood, Am. J. Dis. Child. **23**:316 (April) 1922.

[4] Engman, M. F., and Wander, W. G.: Application of Cutaneous Sensitization to Diseases of the Skin, Arch. Dermat. & Syph. **3**:223 (March) 1921.

[5] Spohn, H.: Canad. M. A. J. **12**:461 (July) 1922.

[6] Shannon, W. R.: Demonstration of Food Proteins in Human Breast Milk by Anaphylactic Experiments on Guinea-Pigs: Their Probable Relationship to Certain Diseases of Nursing Infants: A Preliminary Report, Am. J. Dis. Child. **22**:223 (Sept.) 1921.

who included egg in their diet. These infants suffered from eczema. Discontinuing the offending protein, he contends, caused a disappearance of the eruption occurring in these infants. He further passively sensitized a series of guinea-pigs to egg protein and then caused shock in them by injection of the breast milk of mothers on an egg diet.

Recently, Stewart,[7] using the uterine strip method of Dale, a more sensitive method of producing anaphylaxis in animals, was unable to produce shock in guinea-pigs previously sensitized to egg protein by injection of breast milk from mothers who included egg in their diet. These were mothers of infants who had eczema. The infants all showed cutaneous reactions on application of the egg protein to the skin. He concludes from his work that it is not yet possible to demonstrate that egg protein passes through the mother's milk and sensitizes the infant.

There seems to be an unquestioned relationship between protein sensitization and the eczema of infants and children. However, direct evidence of the allergic nature of infantile eczema has not been demonstrated in all cases.

That the sugar and fats are the offending constituents in the diet in certain cases of eczema cannot be denied. These probably do not act in an allergic manner. All we can say at the present time is that any of the essentials of the diet, protein, fat or carbohydrate in excess, seem to have an influence toward continuation of the eruption. Most workers in this field feel that the protein skin test furnishes useful information as to the treatment of each individual case. The protein to which the child shows a cutaneous reaction should be omitted from the diet. Otherwise, the offending protein should be altered, as infants sensitized to cow's milk protein improve on a diet in which the cow's milk protein has been denaturized in some way, as by pancreatization, boiling or peptonizing. Schloss [2] gives the following summary of his work, utilizing this principle in the treatment of eczema:

1. Treatment by eliminating the foods to which the patient reacts.
2. Treatment by immunization, viz., by feeding gradually increasing amounts of the offending protein or food until tolerance is established.
3. Treatment by desensitization; that is, by hypodermic injections of the protein to which the patient is sensitive.

The most valuable addition to the drug therapy of eczema is the crude coal tar method, described by White.[8] The prescription consists of crude coal tar 2, zinc oxid 2, cornstarch 16, petrolatum 16 gm. It is necessary, first, to mix the cornstarch and petrolatum, and next, to mix the zinc oxid and coal tar, combining these two products as the final thick black paste used in the treatment. This product or paste can be removed from the skin by warm olive oil or mineral oil. Probably its greatest disadvantage is the staining of clothes and bed linen. However, this stain can be removed without injury to the clothing and bed linen. White advises covering both sides of the stained portion of the fabric with lard. This is left on for one hour, and then the cloth is washed with soap and water. By this method, the stain can be entirely removed.

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[7] Stewart, H. C.: Excretion of Foreign Protein in Human Milk, Am. J. Dis. Child. **25**:135 (Feb.) 1923.

[8] White, C. J.: Crude Coal Tar in Dermatology, Arch. Dermat. & Syph. **4**:796 (Dec.) 1921.

URTICARIA

Sidlick and Knowles[3] remark that cutaneous reactions are brought to light when various proteins are applied by cutaneous or intracutaneous tests to the skin of patients subject to urticaria. They tested twelve children having urticaria, and nine of the group reacted to one or more proteins. Three of the subjects were clinically cured. Four were markedly improved by omitting these proteins from their food. The remaining children failed to improve on the restricted diet. Schloss made cutaneous tests on sixty patients with urticaria following regularly the ingestion of some food. In only ten cases were the tests positive. In four cases, it was possible to demonstrate the exact relationship by feeding experiments or immunization. In the rest of the series of cases that showed cutaneous reactions, it was impossible to prove a causal relationship by elimination of the foods in question.

In this disease, as well as in eczema, Sidlick[3] and Knowles remark that correcting the gastro-intestinal abnormalities, if possible, as well as eliminating the offending proteins from the diet, increases the number of clinical cures.

Walker[9] reports five cases of urticaria in children, two of which were caused by horse dander protein and three by ragweed pollen. Treatment by desensitization was satisfactory in these cases.

The occurrence of eczema, urticaria and asthma in the same child has been observed several times. The relationship of food sensitization to urticaria is now definitely established. The method of obtaining clinical improvement in urticaria is the same as that which is given under the outlined treatment for eczema.

PSORIASIS

Jamieson[10] studied the blood nitrogen in fifteen cases of psoriasis. He could not demonstrate any appreciable change in the blood urea nitrogen or uric acid. There was no relationship between the total nitrogen of the blood and the presence or absence of the lesions in the patients studied.

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[9] Walker, I. C.: Eczema from Proteins, J. A. M. A. **70**:897 (March 30) 1918.

[10] Jamieson, R. C.: Experimental Work on Blood Nitrogen in Psoriasis, Arch. Dermat. & Syph. **4**:622 (Nov.) 1921.

Sachs[11] reports favorable results in the treatment of psoriasis with intravenous solution of sodium salicylate. The first injection he gave was 2 gm.; the second injection, 3, and the third injection, 4, which was the maximum dose. Four injections usually suffice. Bravo[12] reports good results with this method of treatment. He uses smaller doses. The first injection was 0.5 gm.; the second injection, 1, and the third, 1.5. He gradually increases the dosage by 0.5 gm. until the dose of 3 or 4 gm. is reached. The interval between the injections is three days.

RINGWORM

Rasch[13] mentions one type of ringworm known as tinea kerion. This is also described by Williams.[14] It is a deep seated, acutely inflammatory process which results in the formation of a rounded boggy, carbuncle-like tumor. The surface of the lesion is reddish or purplish, and is marked by numerous pinhead to split pea size pustules and gaping follicular orifices. The subcutaneous tissue is honeycombed and filled with purulent matter, small amounts of which can be squeezed out through the follicular openings. The tumors may be either single or multiple. They are extremely sensitive to pressure and may give rise to a considerable amount of pain. In addition, there may be pronounced subjective symptoms accompanied by a rise in temperature. As a result of a long continued inflammatory reaction, this type of the disorder may undergo a spontaneous cure.

Cultures have shown that the fungus causing the kerion may be any one of the several species of fungi. There does not seem to be any relationship between the variety of the fungus and the character of the skin eruption. Associated with the kerion, there is often an accompanying exanthematous eruption. The commonest form of the exanthem is an eruption of small lichenoid papules, sometimes occurring singularly, but usually grouped in patches of varying size. Other types of the exanthem have also been noted, such as vesicles, pustules and a scarlatinaform rash.

In patients suffering from kerion, the injection of trichophytin may produce an exanthematous eruption exactly like that occurring in the course of the disease. This eruption also fades as the kerion heals, and if there are any areas of tinea on the skin, these also heal with the fading of the eruption. The eruption is generalized, occurring on the extremities, body and face.

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[11] Sachs, O.: Wein. klin. Wchnschr. **34**:185 (April 21) 1921.

[12] Bravo, J.: Brit. J. Dermat. & Syph. **34**:353 (Nov.) 1922.

[13] Rasch, C.: Brit. J. Dermat. **32**:317 (Nov.) 1920.

[14] Williams, C. M.: Lichenoid Tricophytide, Arch. Dermat. & Syph. **4**:353 (Sept.) 1921.

The first treatment offered is medication. In early cases, this method is efficacious. In more advanced cases, with larger areas involved, medical treatment does not give as successful results.

Elford,[15] also Giffen,[16] has obtained successful results in children who had small patches of ringworm eruption on the scalp. They recommend shaving the head, and then next applying tincture of iodin. The infected areas are then sprayed with ethyl chlorid; the head is covered with a clean cotton cap, and the parents are instructed to shampoo the child's head at night. Treatment is continued each day for two weeks, and then the treatment is modified, according to the apparent progress. The parents are cautioned against the use of any greasy substance or other medication to supplement this form of treatment.

Strickler [17] advises the use of vaccines in the treatment of ringworm. He uses a vaccine made from a grown culture of the trichophyton. This vaccine is used in gradually increased doses. Usually, three injections of the vaccine suffice. Strickler obtained successful results in fifteen children in whom the vaccine was used.

Sabouraud's roentgen-ray technic for the treatment of tinea of the scalp has been improved through the introduction of the Coolidge tube, by which the amount of rays absorbed can be measured with accuracy. Oliver,[18] Lane,[19] Knowles,[20] Graham [21] and Hazen [22] have aided in developing a successful technic for the roentgen-ray treatment of ringworm. They report very successful results with this form of therapy. It may be said that the roentgen-ray treatment of tinea tonsurans is probably the most efficient method of treatment.

IMPETIGO CONTAGIOSA

Knowles [23] divides the eruption of impetigo contagiosa into four types:

1. The common variety, in which the lesions dry up into a yellowish crust and are readily cured with the proper medication.

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[15] Elford, W. P.: Brit. M. J. **1**:867 (June 26) 1920.
[16] Giffen, M. W.: Brit. M. J. **1**:267 (Feb. 18) 1922.
[17] Strickler, A.: J. Cutan. Dis. **33**:181 (March) 1915.
[18] Oliver, E. L.: Boston M. & S. J. **174**:751 (May 25) 1916.
[19] Lane, C. G.: Boston M. & S. J. **183**:673 (Dec. 9) 1920.
[20] Knowles, F. C.: Pennsylvania M. J. **20**:337 (Feb.) 1917.
[21] Graham, J. G.: Brit. M. J. **2**:563 (Sept. 23) 1922.
[22] Hazen, H. H.: J. Cutan. Dis. **37**:307 (May) 1919.
[23] Knowles, F. C., and Munson, H. G.: Institutional Epidemics of Bullous Impetigo Contagiosa, Arch. Dermat. & Syph. **7**:376 (March) 1923.

2. The pustular type, which is in close association with a hair follicle.

3. An outbreak of dime size lesions with yellowish brown or brownish crusts and inflammatory areola—ecthyma.

4. The bullous type, which is usually classified as pemphigus neonatorum.

The usual type of impetigo contagiosa is a disease of children. The bullous form in most instances occurs in infants. Because of the contagiousness of the bullous type of impetigo, this form of the disease is very liable to occur in epidemic form in institutions caring for infants. Numerous epidemics have been reported in the literature, the mortality varying from 30 to 50 per cent.

There has been much discussion regarding the etiologic organism in impetigo contagiosa, as to whether the causitive organism belongs to the staphylococcus or to the streptococcus group. Highman [24] states that the cause of the affection is the streptococcus. Flehme,[25] in fifty-five cases of impetigo contagiosa, which he investigated bacteriologically, found streptococci in pure culture or mixed with staphylococci, according to the age of the lesions. In every case, the organism was of the type *Streptococcus longus.* In man, it was possible, through superficial inoculation of the organism, to form typical lesions of impetigo contagiosa. The organisms were also recovered in pure culture from the lesions produced. In 15 per cent. of normal persons, Flehme was able to culture the streptococci from the skin. The streptococcus closely resembled the organism found in clinical impetigo contagiosa. The superficial inoculation of pure cultures of streptococci recovered from normal skin likewise produced a clinical impetigo lesion.

Flehme [25] believes that the cause of impetigo contagiosa is the attack on fertile ground of a large dose of impetigo streptococci. The normal skin appears to have a resistance to the organism. One may consider the impetigo streptococcus as a semiparasitic organism which, under certain circumstances and with a diminished resistance of the skin, leads to the formation of the disease. In epidemics, there may be an increased virulence of the organism, which overcomes the normal resistance of the healthy skin.

Farley and Knowles,[26] in an extensive study of the bacteriology of impetigo contagiosa, conclude that the streptococcus is the etiologic organism in the common type of the infection. These authors state that, with proper precautions and under proper conditions, streptococci may be obtained from nearly all cases of impetigo contagiosa. If the streptococci are to be obtained on culture, it is necessary to take the material from an early and unruptured lesion. If this is not possible, the culture should be taken from the deep, redder parts of the skin, from which all crusts have been removed. The following strains of the streptococci were found: *Streptococcus pyogenes, Streptococcus anginosus, Streptococcus subacidus* and *Streptococcus fecalis.* Associated organisms, such as staphylococci, pseudodiphtheria bacilli, are either secondary or extraneous invaders. It is not possible to predict from the clinical lesion what type of the streptococcus will be found in the culture.

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[24] Highman, W. J.: Dermatology, New York, The Macmillan Company, 1921.

[25] Flehme, E.: Dermat. Ztschr. **31**:111 (Sept.) 1920.

[26] Farley, D. D., and Knowles, F. C.: Impetigo Contagiosa, Arch. Dermat. & Syph. **3**:753 (June) 1921.

Nothing new has been added to the therapy of impetigo contagiosa. Ammoniated mercury is recognized as specific. An important detail in the treatment by ointments is bandaging of the affected parts. The bandaging keeps the ointment in constant approximation to the lesions, and the end-result is effected sooner.

Morrow [27] uses silver nitrate to abort the early lesions of impetigo. He recommends that the vesicles or pustules be ruptured with gauze and the base of the lesion covered with silver 20 per cent. nitrate solution. When crusts are present, these should be removed also and the underlying base treated with the silver nitrate solution. He uses the same strength silver nitrate solution in infants and reports the same uniformly good results.

SCLEREMA

Lieberthal [28] gives the following classification of sclerema, which has in general been accepted: (1) sclerema adiposum and (2) sclerema edematosum (scleredema or edema neonatorum).

Sclerema adiposum, which is of far rarer occurrence than sclerema edematosum, develops either in the first few days of life, in weakly premature infants with or without internal disease; or later, within the first few months, subsequent to "cholera infantum," enteritis, pneumonia or some other disease. All parts of the body may become affected, except the palms, soles, scrotum and chest. The disease begins as a rule on the lower extremities and rather creeps upward. Its distribution is symmetrical. The skin becomes firm and hard, tightly drawn and firmly united with the subcutaneous tissues and the other structures; in other words, perfectly immovable. The color of the diseased skin is pale, yellowish, waxy or bluish red. The skin feels cold. In an extensive case of sclerema, the infant's body feels like a frozen corpse. The affected parts show no swelling: they are diminished in volume. The extremities are very thin, and the skin gives the impression of being glued to the bone. Active and passive motions are impeded. The pulse is slow and weak, and respirations are shallow and labored. The temperature of the whole body is considerably lowered. The prognosis of these cases which begin in the first days of life is uniformly unfavorable. Within a few days, the disease terminates fatally. Histologically, the affected skin is found contracted, atrophic and anemic.

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[27] Morrow, H.: Impetigo Contagiosa, J. A. M. A. **69**:177 (July 21) 1917

[28] Lieberthal, D.: J. Cutan. Dis. **36**:29 (Jan.) 1918.

Sclerema edematosum (scleredema or edema neonatorum) is observed on the second to the fourth day, rarely later than the fourteenth, in prematurely born, weakly developed infants, and in some cases of congenital syphilis. The disease consists of an intensive edema, which begins as a rule on the feet and the calves of the legs, gradually spreading to the trunk and upper extremities, and, in extreme cases, even to the neck and to the face. The skin shows at the beginning the characteristic red tint of the new born or is cyanotic. With the increase of the edema, the skin appears either pale or more cyanotic. Pitting on pressure disappears slowly. In higher degrees of development, however, there is no pitting, the skin being firm and immovable. There is considerable increase in volume of the parts affected, which produces disfigurement and impedes motion. The skin feels cold and the body temperature is considerably reduced. The children are apathetic. The respirations are weak and slow and the action of the heart is weak. Prognosis in the greater majority of cases is unfavorable. The patients die within a few days. Pathologically, the process is a common edema of the skin, also involving the subcutaneous layer and the deeper tissues. Histologically, the skin does not correspond to that of a normally developed infant, but rather to the skin of a fetus of the sixth to the eighth month.

Earlier writers (Knofelmacher, Sanvorat, Mitchell, Theimich and Jaeckle[29]), analyzing the fat of scleremic infants, advance the theory that there is a loss of fluidity of the body fat and, because of the lowered temperature, sclerema results. Fat is composed of palmitic and stearic acids which solidify at a lower temperature. Oleic acid, which is the liquid fatty acid, is also a component of the fat. The fat of infants normally contains more of the solid fatty acids (palmitic and stearic). These writers believed that in sclerema the proportion of the solid fatty acid (palmitic and stearic) of the tissues was increased and, with the lowered temperature, brought about the hardened condition of the skin.

Smith[30] examined chemically the subcutaneous fat in an infant suffering from sclerema. He analyzed the fat from the normal areas of the skin, also the fat contained in the scleremic area of the infant's skin. He concluded that the subcutaneous fat taken from the scleremic area of the infant's skin had a higher fatty acid content than the subcutaneous fat taken from a normal area of the same infant's skin. There was no indication of any difference in the oleic acid content of the two fats. These findings do not justify a conclusion as to the etiology of sclerema. However, they seem to indicate that the change taking place in the subcutaneous fat is similar to a fat necrosis and not due to the absence of oleic acid.

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[29] Quoted by Smith, C. S.: J. Cutan. Dis. **36**:436 (Sept.) 1918.

[30] Smith, C. S.: Footnote 29.

Pernet [31] reports two cases of partial sclerema occurring in new-born infants. Although neither the clinical findings nor the Wassermann reaction sustained a diagnosis of syphilis as the causitive factor, mercury medication had a favorable effect on the condition, both infants recovering from the disease.

Bourne [32] treated an infant who had sclerema with thyroid extract, one-fourth grain daily, and, with the application of external heat, endeavored to combat the subnormal temperature. The infant improved rapidly during the first month, and, at 6 months of age, no evidence of sclerema remained.

SCLERODERMA

Scleroderma is divided into two main types: (1) the generalized or diffuse type, which may be associated with scleradactylia; (2) the localized or morphea type.

Goodman [33] describes an acute form of diffuse scleroderma occurring in a girl, 9 years old, following an attack of tonsillitis. The skin of the forehead, scalp, back of the neck and shoulders, as low as the spines of the scapulae, the cheeks, the chin and the neck as far down as the clavicles was most markedly affected. The eyelids drooped, appeared stiff and gave the child an inattentive and stupid expression. There were no wrinkles in the skin, which was warm and dry, felt thickened but inelastic and had a boardlike hardness. It was not possible to pinch up any skin between the thumb and forefinger. There was no pitting on pressure. The forehead could not be wrinkled, nor could the lower eyelids be retracted downward. The mouth could be opened only partly. The child was unable to whistle. Active and passive movements of the head, extension, flexion, lateral flexion and rotation were limited. During four weeks' stay in the hospital, the child failed to improve. She was given daily oil rubs. Thyroid extract in one-fourth grain doses daily was administered by mouth. She was then discharged from the hospital under the same treatment. Four months after her discharge, her appearance had changed considerably. She was brighter. The skin of the scalp retained its hardness and immobility, but the eyelids and cheeks were soft and pliable and the hardness of the rest of the skin was gone.

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[31] Pernet, G.: Brit. J. Child. Dis. **15**:218 (Aug.) 1918.

[32] Bourne, E.: Lancet **1**:368 (Feb. 25) 1922.

[33] Goodman, H.: Jour. Cutan. Dis. **6**:210 (April) 1918.

Weidman [34] described a case of congenital scleroderma and sclerodactylia occurring in a new-born infant. The interesting factor in this case is the age of the child. Histologic study of the skin led Weidman to this diagnosis, as the microscopic picture clinically resembled that found in scleroderma of childhood and adult life.

Aronstam [35] reports a case of scleroderma in a girl, 15 years old. At 7 months, she fell and struck the right arm. At the time of the injury, no lesion was noticeable except a mild ecchymosis, which subsided in two weeks. Two months after the injury, a sclerotic patch appeared at the site of the trauma, which rapidly spread upward toward the middle third of the arm and downward to within 1 cm. of the metacarpus. Clinically, the lesions were waxy, yellowish brown, livid areas and bands longitudinally arranged along the extensor surface of the right arm. The skin was rigid and tightly bound down to the underlying structure. The cutaneous sensibility was normal.

Regarding the etilogy of scleroderma, Foerster [36] believes that there is reasonable evidence for attributing an important part in the etiology of scleroderma to morphologic and functional changes in the internal secretory organs, especially the thyroid gland. This newer idea would seek to displace the accepted view that scleroderma is an "angiotrophoneurosis."

The consensus of opinion today, in reference to the etiology of scleroderma, is that the affection is at least closely related to disturbances of function or "unbalance" of secretion of one or more of the ductless glands. Supporting this idea is the report of a case of scleroderma by Shamberg [37] occurring in a child who was a cretin.

A great many of the cases of scleroderma follow colds and exposure to wet and draughts. A history of preceding tonsillitis is given in many of the recorded cases.

Berrheim-Karrer [38] describes five cases of necrosis of the subcutaneous tissues in the new-born (so-called scleroderma of the new-born). A common feature of all his cases is the occurrence of infiltration in the deeper layers of the skin. The favorite sites are the back, outer surfaces of the arms, cheeks and chin. The size varies from that

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34. Weidman, F. D.: Necropsy Findings in Case of Congenital Scleroderma and Sclerodactylia, Arch. Dermat. & Syph. **1**:375 (April) 1920.

35. Aronstam, N. E.: Urol. & Cutan. Rev. **26**:77 (Feb.) 1922.

36. Foerster, O. H.: J. Cutan. Dis. **34**:1 (Jan.) 1916.

37. Shamberg, J. F.: Tr. Am. Dermatol. Ass'n, June, 1919.

38. Berrheim-Karrer: Schweiz. med. Wchnschr. **52**:12 (Jan. 5) 1922

of a lentil to that of a plate. The author observed these nodes twice on the seventh day, once on the eighth day, once on the eleventh day and once on the thirteenth day after birth. The author never observed scar formation in contrast to atrophy in genuine scleroderma. Disappearance of the nodes occurred between the twenty-eighth and sixty-ninth day after birth. Microscopic examination proved the lesions to be in the subcutaneous fat. No bacteria could be found. The fatty tissue was strikingly rich in cells and network. The necrosis was limited to the individual fat cells. The characteristic structures of the fatty tissue were completely lost and some areas did not even reveal the presence of septums. This scleroderma of the new-born is a fatty necrosis of the subcutaneous fatty tissues. There is a marked clinical and histologic difference between the genuine scleroderma and this form.

Brinchmann [39] reports a case in a boy, 5 weeks old, who was born in a state of asphyxia. He had extensive thickening of the subcutaneous tissues, on the extremities, the thorax and the back. They were not prominent over the level of the skin. The temperature had always been normal, as well as the body functions. The subcutaneous prominences disappeared slowly, so that, after a period of five or six months, they were no longer visible. The histologic examination of a specimen of the skin disclosed amorphous masses in the subcutaneous fat lobules. There were no degenerative processes. The amorphous masses were formed of calcium as revealed by the silver nitrate coloration with Hubschmann's reagent and by the addition of hydrochloric acid. The author called this condition sclerema neonatorum. However, he remarks that it is not true sclerema, as is shown by the normal temperature, and the normal body functions, in addition to the fact that true sclerema is fatal. This case presented a condition somewhat similar to that reported by Berrheim-Karrer,[38] with skin manifestations clinically resembling scleroderma. Careful study, however, reveals that these cases present separate entities.

ACRODYNIA: ERYTHREDEMA, PINK DISEASE AND EPIDEMIC ERYTHEMA

Bilderback [40] described six children with a disease characterized by profuse sweating without odor, with swollen red feet and hands that are painfully sensitive to the touch. The hands and feet are cold and clammy, and the skin of the hands and feet are in the state of desquamation. The body, legs and arms may or may not have a rash. The rash is similar to an erythema or intertrigo that at times borders on an eczema and itches. Added to the local symptoms, there is a progressive loss of weight and marked weakness and apathy that at times approaches stupor. Bilderback [41] gave no specific name to this disease in his initial report.

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[39] Brinchmann, A.: Norsk. Mag. f. Lægevidensk. **83**:269 (April) 1922.

[40] Bilderback, J. B.: Northwest M. J. **19**:263 (Oct.) 1920.

Byfield,[42] in an excellent treatise, reported seventeen similar cases in children, all under 4 years of age. He remarks that the disease has a close resemblance to pellagra, but that so many manifestations argued against such a diagnosis that it was necessary to consider the possible presence of some other disease.

The clinical picture as given by Byfield is a complex one, the nervous system and the skin being the most involved. Respiratory and digestive tracts are less affected. In the nervous system, the changes are chiefly sensory or atrophic in character. Alopecia and pulling out of the hair occur in some cases. Falling out of the teeth, with only slight involvement of the gums, photophobia and, in one case, neurokeratitis were seen. Changes in the nails and reddening of the tongue also occur. Paresthesia of the toes and feet and of the fingers and hands was another constant and often most distressing symptom. The reflexes are diminished in almost all cases and absent or increased in some. Dullness and apathy, alternating with extreme restlessness and sleeplessness, were observed. In a characteristic case, the patient would often adopt an atypical posture, either lying on the side, rubbing the hands or feet, or crouching with the head buried in the pillow.

The skin manifestations are uniform. A symmetrical involvement of the fingers and toes, recurring at intervals of a fortnight or so, or even tending to be more or less constant, was one of the most striking characteristics of the disease. With the hands and feet cyanotic and cold, there appeared a non-confluent erythematous rash, most marked at the tips of the fingers and gradually diminishing until, at the region of the wrist, it had quite faded away. In some cases, a small number of fine papules rose from the area of erythema. Confluent erythema was the rule on the distal phalanges. Desquamation, most marked at the tips of the fingers and toes and growing less toward the region of the wrists and ankles, was often present. The feet were only slightly less involved than the hands. Never was there observed anything like a clean cut line of demarcation between affected and untouched skin as is seen in pellagra. When the thorax or approximate portions of the arms and legs showed skin manifestations, these consisted in either a morbilliform breaking-out or bullae, the latter being seen only in severe and more advanced cases.

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[41] Dr. J. B. Bilderback of Portland, Ore., was the first author to describe acrodynia in this country. The description of his cases was sent by his associate, Dr. Patrick, to Dr. Weston of Charleston, S. C., who suggested the name acrodynia for this condition.

[42] Byfield, A. H.: A Polyneuritic Syndrome Resembling Pellagra-Acrodynia (?) Seen in Very Young Children, Am. J. Dis. Child. **20**:347 (Nov.) 1920.

When an eruption appeared on the body, it was usually accompanied with paresthesia. When the eruption disappeared, pigmented spots were sometimes left. In two cases, the cheeks and the tip of the nose were involved. The nails are rarely involved.

An extreme and obstinate anorexia was the prominent feature of the disease. Failure to take a sufficient quantity of food would seem to be responsible for the marked degree of emaciation which is almost invariably present in these children who have been sick for several months. Many of the patients suffered extreme thirst. Unusual sweating was common in more advanced cases.

Frequency of urination was an almost uniform symptom. This was probably accompanied by distress, as many of the children continually complained of a desire to empty the bladder. Pyelitis was frequently present, though it was never extreme and readily yielded to treatment.

In a study of the diets of these children previous to development of the disease, no connection could be established between the previous diet and the onset of the disease.

A postmortem examination was made in one case, observed by Byfield. There were interesting changes present in the central nervous system. In the spinal cord, gliosis about the central canal was found. Some of the anterior horn cells proximal to the anterior commissure were found to be of poor staining quality. The sciatic nerve showed edema and swelling of the myelin sheath, as well as of the connective tissue about the nerve fibers. No cellular infiltration was observed. The same variation in the size of the fibers was seen in the posterior roots in the lumbar cord. Edema and swelling of the myelin sheath were also seen in the fibers of the dorsal root in that portion of the nerve lying between the ganglion and the spinal cord.

Since these original papers, numerous observers, Emerson,[43] Cartin,[44] Zahorsky,[45] Wood,[46] Weber,[47] Field,[48] McNeal,[49] Thursfield,[50] Davis,[51] Vipond,[52] Porter,[53] and Lindsay[54] have reported cases of

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43. Emerson, P. W., and Green, H.: Acrodynia, J. A. M. A. **77**:285 (July 23) 1921.
44. Cartin, H. J.: Pennsylvania M. J. **24**:287 (Feb.) 1921.
45. Zahorsky, J.: Mississippi M. A. J. **18**:153 (May) 1921; Semeiology of Pink Disease (Erythredema, Acrodynia), J. A. M. A. **79**:1975 (Dec. 9) 1922.
46. Wood, A. J.: M. J. Australia **1**:145 (Feb. 19) 1921; Am. J. Trop. Med. **1**:291 (Sept.) 1921.
47. Weber, F. P.: Brit. J. Dermat. & Syph. **33**:228 (June) 1921; **34**:111 (April) 1922.
48. Field, M. C.: Arch. Pediat. **39**:116 (Feb.) 1922.
49. McNeal, M. D.: Minnesota Med. **5**:153 (March) 1922.
50. Thursfield, H., and Paterson, D.: Brit. J. Child. Dis. **19**:27 (Jan.) 1922.
51. Davis, C. M.: Arch. Pediat. **39**:611 (Sept.) 1922.
52. Vipond, A. E.: Arch. Pediat. **39**:699 (Nov.) 1922.
53. Porter, L.: M. Clinics. N. America **6**:431 (Sept.) 1922.
54. Lindsay, L. M.: Canad. M. A. J. **12**:618 (Sept.) 1922.

acrodynia from various parts of the country and abroad, showing the wide distribution of the disease.

There is no specific treatment for acrodynia. A rational diet with hygienic measures gives the best therapeutic results.

PERLÈCHE

Perlèche is described by Smith,[55] also by Lane.[56] It is preeminently a disease of infancy and childhood. It is an affection of the labial commissures, almost always bilateral, and usually rather closely limited. As it progresses, the process extends for a varying distance toward the center of the lips, and usually extends a little way onto the skin surfaces and the true mucous membrane of the inner side of the lips. At the beginning of the disease, the epithelium is smooth and whitish, with a mother-of-pearl tinge. As it progresses, the epithelium becomes macerated and a little thickened, and loses most of the mother-of-pearl color. Small transverse fissures appear, which show a red base, if the lips are stretched, but do not reach the lower layers of the epidermis, and do not bleed easily even if rubbed. In some cases, there is slight erosion, but the surface is ordinarily not denuded. It is never an ulceration, and there is no swelling of the lips connected with it. There is little or no inflammatory area around the lesion. As the lesions begin to heal, their appearance approaches that of the early lesions, and after the roughness has disappeared, there remains only a slight discoloration, which persists for a month or so. No scars are left. If treated, the disease is usually cured in two or three weeks. If left to itself, there is usually spontaneous cure in a month or so, unless there is reinfection; but, in some cases, it is of indefinite duration.

In the mild cases of perlèche, there are no subjective symptoms at all. In the fully developed cases, there is a slight feeling of irritation, which causes the child to run the tongue over the lesion. It is probably from this sign that the disease develops its name (perlèche, meaning "licked"). There is never enough discomfort to cause the child to rub or pick the lesions. There are no other lesions or physical signs. There is never more than the slightest inflammatory reaction. The lymphatic glands are never enlarged.

Streptococcus plicatilis is probably the causative organism, although the disease has not been successfully reproduced in animals or human beings with this organism.

Auche[57] studied the histopathology of one case of perlèche and found cellular infiltration of the connective tissue of the papillae, dilata-

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55. Smith, A. L.: Arch. Pediat. **34**:274 (April) 1917.
56. Lane, J. E.: Perlèche, J. A. M. A. **69**:192 (July 21) 1917.
57. Auche, quoted by Lane, J. E.: Footnote 56.

tion of the blood and lymphatic vessels, thickening of the interpapillary plugs, enlarged intercellular spaces in the prickle cell layer, with leukocytic infiltration, and in the upper part of this layer, serofibrinous infiltration and some intercellular cavities filled with polymorphonuclear leukocytes. Some of the prickle cells were degenerated, opaque and without nuclei.

Perlèche is highly contagious. Common drinking utensils are the most frequent vehicles of transmission. Other ways in which it is spread is by kissing and the use of common pencils, handkerchiefs and towels.

The treatment is simple. Prompt cure is affected by painting the lesions daily or every other day with a 10 per cent. solution of silver nitrate or a diluted tincture of iodin.

CUTANEOUS TUBERCULOSIS

Wise and Satenstein [58] describe the clinical and histologic feature of papular necrotic tuberculids, together with the presentation of two cases occurring in children. They mention the occurrence of folliclis, acinitis and lupus erythematous in association with the papulonecrotic tuberculids, which are relatively common. It is conceded by the majority of the prominent workers in the field of dermatology that folliclis and acnitis are two more or less similar clinical manifestations of one or the same dermatosis. Folliclis is the more superficial form. It appears as necrotic papules, most frequently on the back of the fingers and hands; on the palms at times; on the ulnar surface of the forearms, and about the points of the elbows. It often attacks the skin of the trunk and the lower extremities.

Acnitis is the deeper form, the necrotic papules affecting chiefly the face. The eruption on the hands is frequently associated with periones of the fingers, or merely the acro-asphyxia and an eruption of facial lupus erythematous. Among the modern writers, there is a growing tendency to regard folliclis and acnitis as so closely related nosologically that the same interpretation of the pathogenesis is applicable to both types of eruption. While there seems to be a practically unanimous agreement as to the tuberbacillary nature of folliclis, the same unanimity of opinion does not obtain with regard to acnitis. The consensus of opinion is that, while folliclis is always a tuberculous disease, acnitis may be at times a tuberculous manifestation, at other times nontuberculous, very much as is, presumably, the case with lupus erythematous. The clinical observer cannot ignore the patent fact that a majority of patients presenting the papulonecrotic lesions of folliclis on the upper extremity have also a papulonecrotic eruption on the face.

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58. Wise, F., and Satenstein, D. L.: Clinical and Histologic Features of Certain Types of Cutaneous Tuberculosis, Arch. Dermat. & Syph. **4**:586 (Oct.) 1921.

The pathogenesis of the papular necrotic tuberculids and the associated conditions—folliclis, acnitis and lupus erythematous—has caused spirited controversy. The pathogenesis of these eruptions is still a partly unsolved problem. The tuberculids have been defined as "local reactions wherein nature has set up a cutaneous reaction, which indicates the response of the skin to the products (or derivatives) of tubercle bacilli." Zieler[59] regards them as "reactions of cutaneous hypersusceptibility in tuberculous individuals, provoked by disseminated tubercle bacilli, these reactions as a rule leading to the destruction of metastasizing tubercle bacilli." The modern conception postulates the existence of a hematogenous tuberculous infection. It is presumed that the lesions result from the activity of isolated tubercle bacilli, occurring in scant numbers in the skin. The bacilli circulating in the blood stream ultimately find a resting place in the blood vessels of the cutis, there to be subjected to the action of the various antibodies, finally undergoing lysis, and liberating certain toxins, which presumably play a part in the formation of the papulonecrotic lesions.

The histopathologic study of acnitis and folliclis reveals few very typical changes, whether the tissue is obtained from fresh or from old papules. Most of the sections show merely the ordinary alterations which characterize inflammatory tissue; namely, cell infiltration, consisting of numerous round cells and few plasma cells. These infiltrates, occurring frequently about the sebaceous and sweat glands, undergo a slow process of necrosis. Involution takes place after spontaneous extrusion of the broken down mass. The lesion heals, leaving a deep, sharply defined round scar, often surrounded by a zone of pigmentation. On the other hand, the presence of epithelioids and giant cells has been observed by several investigators. Briefly stated, it may be said of the papulonecrotic tuberculids that, in the present state of our knowledge, the clinical diagnosis has far more weight than the histologic.

According to Lewandowsky,[60] the simplest histologic change in the papulonecrotic tuberculids, as is the case in all other hematogenous tuberculosis of the skin, consists of a circumscribed infiltrate of tuberculoid structure in the cutis. Often the microscopic appearances present little or no evidences of a tuberculous structure, the usual findings being those corresponding to an ordinary reaction in the skin. But those investigators who have had the opportunity to examine a large number of sections, obtained from various types of lesions, have on numerous

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59. Zieler: Die Tuberkulose der Haut, in Jesionek's Haut und Geschlechts-Krankheiten, 1914, quoted by Wise: Footnote 58.

60. Lewandowsky: Die Tuberkulose der Haut, Enzyklopaedie der klinischen Medizen, Berlin, 1916, quoted by Wise: Footnote 58.

occasions demonstrated in the cutis many small areas containing large giant cells, together with collections of epithelioid cells, so suggestive of tuberculosis. The most characteristic feature, however, is the necrosis. Small areas of necrosis may occur in any portion of the cutis, the surrounding tissue exhibiting a narrow band of epithelioid cells and lymphocytes. Such areas of necrosis are often observed in the upper portion of the corium, just beneath the epithelium, the latter taking part in the destructive process. On either side of the necrotic area, the epithelium shows evidences of proliferation, with edema, hyperkeratosis, and parakeratosis of the epidermis.

The first case presented was that of a girl of 13 years. She had the characteristic patch of lupus erythematosus over the dorsum of the nose. The color of the lesion varied through all shades of inflammatory red. There were fine scales, grayish to grayish yellow, rather scant, and most pronounced over the border. On the cheeks, in the shape of the wings of a butterfly, were numerous small necrotic papules, the so-called "acnitis." The lesions were dull red, resembling the papules seen in variola, and having a necrotic center. There were also some small soft scars present. The scars did not seem to have the tendency to contract and cause disfiguration. Over the dorsum of the fingers were several similar lesions, typical "folliclis." The child appeared healthy otherwise. There was no other evidence of tuberculosis on physical examination. The second case, in a boy, 11 years old, who had many necrotic papules over the anterior surface of the thighs and legs, presented papules, most numerous in the region of the knees, sharply defined, dark red, and having necrotic centers. There was no scarring present at this examination. The rest of the cutaneous surface was free from lesion. These were frank papulonecrotic tuberculids.

Wise and Satenstein[60] state that the appearance of tuberculids in infants and young children points to the existence of visceral tuberculosis, and is therefore of grave significance, especially since the cutaneous eruption is often the first manifestation of the infection and hence may be a valuable warning signal. The concomitance of cutaneous tuberculids and phthisis, tuberculous adenitis and other manifestations of visceral or bone tuberculosis is quite common. Sales[61] reports a case of papulonecrotic tuberculids in a child, aged 2 years. The necrotic papules were followed by fatal miliary tuberculosis. Inoculation of guinea-pigs with tissue consisting of the necrotic papules produced tuberculosis in the guinea-pigs.

Stokes[62] remarks that he has been fortunate in securing fairly successful results by the use of arsphenamin in the treatment of papulonecrotic tuberculids. The technic and dosage are essentially the same as those employed in the treatment of syphilis. The effect is nonspecific and consists in an elevation of the general resistance of the patient rather than in any parasiticidal action on the tubercle bacilli.

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61. Sales, G.: Arch. de méd. d. enf. **25**:513 (Sept.) 1922.
62. Stokes, J. H.: Northwestern Med. **20**:79 (April) 1921.

Cowie[63] reports a case of granuloma rubra nasi—tuberculosis cutis—occurring in a boy, 4 years old. The boy was markedly underweight and had never made the normal average gain in weight even as an infant. He was brought to the hospital on account of redness of the nose, developing in early infancy and persisting ever since. The child presented, over the chest, arms and abdomen, an eruption which consisted of small dusky red papules. There was no weeping at any point. There was no eruption over the face similar to that seen on the body. The eruption or process on the nose was quite different. The entire nose was red, the redness being accentuated at the tip. On close examination, there were many small papules which, when pressed with a glass slide, showed minute yellowish brown points, the so-called apple jelly nodules of cutaneous tuberculosis. The hands and wrists were red, beginning at the tips of the fingers. The redness continued up to the middle of the forearm. There were no abrasions of the finger tips. The child did not put the fingers in the mouth, nor did he seem to exhibit any evidence of pain in the fingers or toes.

The absence of paresthesia was an important differential point in ruling out acrodynia as a diagnosis in this case. An interesting feature of the case was the absence of a positive cutaneous tuberculin reaction. However, this is not unusual, as the marked degree of undernourishment would explain the absence of a positive test.

Sillians[64] presented a Polish boy of 10 years, who had tuberculosis verrucosa cutis, lupus vulgaris and lichen scrofulosorum. The lesion appeared on the foot shortly after birth and spread upward, taking the form of a raised warty looking mass and papillary projections, mostly crusty, with no ulceration or moisture. Roentgen-ray treatment made the lesions tender and moist. Further reaction caused an itching eruption on the body (lichen scrofulosus).

All this is symptomatic of a group of tuberculous skin lesions. Tubercle bacilli of attenuated virulence have been found in tuberculosis cutis and lupus vulgaris. Reactions to tuberculin have produced lichen scrofulosus, as the roentgen ray did in this case. The Pirquet reaction is negative because of the formation of antibodies. There was no scarring in this patient; but the prognosis for recovery is only fair. Treatment consists of judicious use of the roentgen ray.

ICHTHYOSIS

Thibierge and Legrain[65] present three cases of fetal ichthyosis. The disease was first manifested at birth or within the first few months of life. Other congenital malformations have been met in conjunction with the ichthyosis. The hyperkeratosis seen in these cases seemed peculiar to each of the body regions. There was an associated seborrhoea of the hairy scalp in one case. Erythoderma was observed in one case of the series. Fetal ichthyosis constitutes a very precise pathologic type. The cause of the affection remains obscure. The

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63. Cowie, D. M.: M. Clinics N. America **6**:1301 (March) 1923.

64. Sillians, A. W.: Internat. Clinics **2**:32, Series 31, 1921.

65. Thibierge, G., and Legrain P.: Ann. de dermat. et syph. **2**:337 (Aug.) 1921.

fact that syphilis may be a concomitant disease does not render it any easier to determine whether or not syphilis is an etiologic factor.

Jordan[66] observed two cases, one of which was true ichthyosis congenita. The other, which the author considered a milder type of ichthyosis congenita, and which was designated ichthyosis larvata, appeared at first to be ichthyosis congenita. However, under treatment, the skin softened, and after all of the cutaneous phenomena disappeared, the condition resembled ichthyosis larvata. The histologic picture of both conditions is similar: hypertrophy of the superficial epithelium and excessive development of the sweat glands. In ichthyosis larvata, the changes are of a milder type. DeStefano[67] reports a case of congenital ichthyosis in an infant who is now 3 months of age. He believes the condition to be of syphilitic origin, as both the father's and mother's blood gave markedly positive reactions. Henrichsen[68] also reports a case of congenital ichthyosis in a child who died at birth. The entire body was affected so that the body functions were markedly altered.

McGlasson[69] presents two cases of onychogryposis hysterix and keratosis follicularis, occurring in two brothers, aged 17 and 11 years. Except that they were both undersized, physical examination was negative. They were well developed sexually. The clawlike nails of the fingers and toes varied from 2 to 5 cm. in thickness, the degree of deformity corresponding to the proportionate size of the nails on the different toes. The deformity interfered with walking or wearing shoes. Ichthyosis was most marked on the flexure surface of the arms, around the neck and over the abdomen. Keratosis follicularis was more evident on the extensor surface of the arms and legs and in the scapular region. The Wassermann reaction was negative. The older boy was of the moron type. The younger boy was very bright. Surgical extirpation was performed in each case. In the older boy, the nails regained their former condition; in the younger, there was 50 per cent. improvement in new nails. The better method of treatment is the employment of actual cautery to destroy the matrix. The body lesions responded best to applications of boric acid and white petrolatum. This loosens the skin and softens the horny plugs so that they come away easily. As the condition is congenital, treatment must be continued indefinitely.

Mackee and Rosen[70] gave a description of the clinical picture of erythodermia congénitale ichthyosiforme, and presented a child, 14 years old, who had this condition.

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66. Jordan, A.: Dermat. Wchnschr. **74**:585 (June 24) 1922.
67. DeStefano, O. S.: Pediatria **30**:672 (July 15) 1922.
68. Henrichsen, J.: Ugesk. f. Læger **84**:1277 (Sept. 28) 1922.
69. McGlasson, I. L.: Texas State J. Med. **17**:255 (Sept.) 1921.
70. Mackee, G. M., and Rosen, I. R.: J. Cutan. Dis. **35**:235 (April) 1917.

The condition is present at birth in the majority of the cases or develops shortly afterward. Heredity does not appear to play an important rôle. It is about equally common in the two sexes. As a rule, the disease begins with a more or less generalized erythrodermia, which may be marked or inconspicuous. A thickening of the horny layer may precede the erythema. As the patient grows older, the reddened area becomes thickened and scaly, while the erythrodermia is likely to fade gradually and may disappear entirely in adult life. The ichthyotic skin remains, although it too may undergo some improvement. The face is usually red and slightly scaly. Ectropion may be present. The scalp is usually seborrheic.

There are two general types of the affection; namely, the dry type and the bullous type. The former has already been outlined. The same description will answer for the bullous type, with the exception that there are outbreaks of the bullous lesions. The bullae occur most frequently on the extremities. They are very flaccid and disappear without producing scars.

The disease is usually generalized and symmetrical. Cases have been described, however, in which there are circumscribed, symmetrical lesions. In some instances, the lesions are sharply marginated. In others, the margins are not closely defined. Perspiration does not occur over the general cutaneous surfaces, but there may be hyperhidrosis of the palms and soles. The general health is unimpaired, and there are no objective symptoms, with the exception of more or less pruritis in some of the cases.

An erythrodermia congénitale ichthyosiforme seen in a 14-year-old girl was first noticed at 5 months, when red areas developed here and there over the body. A few months after the onset of the erythema, the lesions became scaly. Later, the thickening of the skin was a marked feature, so that by the fifth year the affected areas of the skin were thickened and dark brown or black in color. The eruption occurred in remissions, the skin improving during the summer months. The etiology of this condition is obscure. Nothing is offered in the form of treatment.

MISCELLANEOUS DISEASES

Weber [71] describes a child, aged 4, with a congenital hypertrichosis or hirsutes. The hypertrichosis affected the forehead, temples, sides of the face, the back and the upper and lower extremities. The regions of the groins, pubes, front of the trunk and the neighborhood of the mouth and nose are not hairy. There was nothing to suggest the presence of a hypernephromatous tumor in the abdomen, and a roentgenogram of the base of the skull showed nothing abnormal about the pituitary fossa. There is no sign of any precocious or abnormal sexual condition. There was no evidence of congenital syphilis. The Wassermann test was negative.

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[71] Weber, F. P.: Brit. J. Child. Dis. **14**:272 (Oct.) 1917.

Weber [71] mentions two types of hypertrichosis, the first of which is termed the "simian type," in which the hypertrichosis is congenital or developmental and sometimes familial and is regarded as an example of the so-called "degenerative reversion." The second type is associated with, and secondary to, disorders of the endocrine organs.

Hutchinson [72] presented an infant, 4½ months old, having numerous nodules scattered over the face, head, ears, body and legs and one on the palm of the right hand. The nodules were situated in the skin and varied in size from a pinhead to a 5-cent piece. They also varied in color from light yellow to brown. There was no tendency to breaking down. The physical, blood and serologic examinations were negative. A nodule was studied by microscopic examination, and Hutchinson concluded that these tumors were multiple primary carcinoid of the skin.

Blaisdell [73] reports a case of congenital alopecia in a child of 4 years. The boy's history, familial and personal, showed nothing of interest. The physical examination was negative. Owing to the baldness, the boy had the appearance of an elfish old man, so characteristic of those without hair either on the scalp or on the face. The hair on the scalp was extremely scanty, consisting of thin straight shafts about one-half inch (1.3 cm.) apart and 1 inch (2.5 cm.) long. The scalp itself appeared to be decidedly parchment-like owing to the lack of subcutaneous fat. The eyebrows were represented by from six to ten small lanugo hairs. The interesting feature of the boy's skin was the asbolute lack of any hair follicles and the extreme dryness of the skin, as the result of the deficiency in the sebaceous and sweat glands. The child suffered no objective symptoms. The important and striking features of the case, based on a careful microscopic study of ten serial sections from different parts of the skin, was the comparatively few blood vessels. Only one erector pili muscle was seen. There were no hair shafts and no sebaceous or sweat glands.

Smith [74] observed a girl, aged 8, with an extensive pigmented and hairy nevus associated with molluscous tumors. At birth, the face, trunk and limbs were covered with dark reddish brown marks, which had since grown in proportion to the growth of the child. At the present examination, almost the whole of the cutaneous surface was covered with pigmented patches, varying in color from reddish to

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72. Hutchinson, W.: J. Cutan. Dis. **31**:161 (Feb.) 1913.
73. Blaisdell, J. H.: Boston M. & S. J. **176**:210 (Feb. 8) 1917.
74. Smith, W. M.: Brit. J. Child. Dis. **12**:299 (Sept.) 1915.

blackish brown. Some of the patches were covered with long and abundant hair, while others were smoother and showed shorter hair.

The skin of the back, especially along the spine, showed a dark pigmentation and was covered with long coarse hair. The skin of the left leg was also dark and hairy, both front and back. In the unaffected areas, which are chiefly seen on the forearm and back of the right leg, the skin was in excellent condition.

On the left arm and leg, which were thinner than the right, the lesions were more pronounced than on the opposite side. The left arm was wasted, and here the whole of the skin was diseased and resembled a monkey's skin in texture.

In addition to the nevi, the child presented a number of molluscous tumors. The largest, which was about 4 inches (10 cm.) long, was attached to the inner side of the left buttock and perineum on the left side. This tumor was divided into two lobes by a fissure midway along the perineum. There was a second tumor, external and inferior to the larger one, in the midline of the left buttock.

Apart from the skin condition and the difference in the size of the limbs on the two sides, the child presented no abnormalities.

The presence of the pigmented and hairy nevus is not uncommon. A similar condition was reported by Fox [75] in 1912.

Nass [76] describes a case of keratoma palmare and plantare hereditarium in a boy, aged 14 years, which developed on the fingers when the patient was 3 months old. At the time of the present examination, it involved both the hands and feet. The affection consisted of thickening of the horny epidermis which formed plates from the thickness of a finger nail to an eighth of an inch or more. The finer markings on the palms and soles were obliterated, while the coarser markings were deepened. The borders of the plates were sharply defined and without inflammatory areola. This is a rare disease. An interesting feature in this case is that there was an area on both forearms about 3 fingers wide of extra sensibility to pain and to the faradic current. The central nervous system presented nothing noteworthy. The lesions themselves were hyperalgesic. The histologic picture showed, in addition to the marked increase of the horny layer of the skin, the presence of streptococci, a feature that had never been noticed before.

Borghoff [77] describes a case of Darier's disease, an unusual skin manifestation characterized by the occurrence of a follicular keratosis, with a peculiar histologic picture. Borghoff gives a description of the

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75. Fox, Howard: A Case of Extensive Pigmented and Hairy Nevus, J. A. M. A. **58**:1190 (April 20) 1912.

76. Nass, H.: Dermat. Ztschr. **33**:338 (July) 1921.

77. Borghoff, J. A.: Darier's Disease in Infant, Arch. Dermat. & Syph. **4**:609 (Oct.) 1921.

first case in which the onset occurred in an infant, who, at the age of 4 months, presented an eruption over the upper portion of the back. This spread slowly in all directions and within three weeks had reached the size of the palm. About this time a similar eruption appeared on the anterior surface of the chest, and this also spread slowly. In three weeks, the condition had become rather widespread, involving the greater part of the back, chest and abdomen, the scalp being also affected at this time. Simultaneously with the appearance of the eruption, the child became extremely fretful during the act of defecation, at times refusing to move the bowels.

On examination, the anus was found to be involved in the general eruption. Over occiput and symmetrically over both temporal regions were many discrete, follicular, pinhead sized papular lesions of a yellowish brown, the majority of which were covered with a dirty brown or black greasy scale. These scales were particularly in evidence over the occiput. On removal of the scale, it was seen to consist of a thick horny plug which extended into the follicle, the papule being left with a minute funnel shaped depression in the center. Though discrete, the individual papules were rather closely aggregated, the scale formation over several of the papules giving the eruption a confluent appearance. A similar condition existed over the entire back and anterior surface of the chest, extending onto the abdomen and into the lumbar region. The lesions over the back and abdomen stood out as more characteristic papules than did those of the scalp. In the axilla and inguinal regions were a number of lesions which had become ulcerated as the result of the moisture and friction. The pruritis at times was intense, preventing the child from sleeping. On the hard palate, 0.5 cm. within the margins of the teeth, were a number of white papular lesions, firm to pressure and the size of a wheat seed. Those posteriorly were ulcerated and covered with a gray membrane, resembling the moist papules of a syphilid. They were symmetrical in their distribution and painful on manipulation.

At the mucocutaneous border of the anus, there was a distinct circular formation of papular efflorescences, each papule of an oval shape and the size of a wheat grain. They were arranged end to end, and were yellowish red, slightly infiltrated and very tender to the touch, causing much pain on defecation. Two of the lesions had become vegetative and presented an ulcerated flat surface.

The skin tissue, showing the more characteristic types of follicular papules, was excised from the scapular region and abdomen. The epidermis presented many changes from the normal. The horny layer was most involved, presenting a marked hypertrophy and a parakeratosis. In that portion nearest the rete were numerous cells which had retained their nuclei, the latter being larger in many instances than those of the prickle cells. The condition was treated by the roentgen-ray therapy. This form of treatment is only palliative. The disease improved for a while; but finally the lesions became ulcerated, secondary infection set in and the child died. The cause of death could not be ascertained.

Abt [78] reports a case of congenital skin defect in a new-born infant who presented a defective skin area over each knee, 1 by 1¼ inches (2.5 by 3.1 cm.). They were symmetrical; that is, they were almost identical in size and shape, and seemed to be irregularly punched out. The skin around the edges was drawn and puckered, presenting the appearance of ulcers with irregular borders. The base was beefy red and moist. From week to week, the ulcers gradually covered over so that, after five or six weeks, the denuded red areas were replaced by shiny, white patches, somewhat lighter in color than the surrounding skin. The healing process was complete, and the baby seemed well in every respect.

The congenital skin defects are attributed either to errors in development or to inflammatory adhesions between the external layers of the skin and the amnion. At the point where this adhesion has taken place, the growth of flat epithelium is retarded. As the liquor amnii accumulates, the so-called Simonart's threads are formed. These are adhesions that form threads or bands between the amnion and the fetus. If these bands are torn loose from the integument of the fetus, a skin defect remains. Not infrequently, these skin defects are associated with other congenital malformations; for instance, deformities of the extremities, such as deficient fingers, hands or feet.

Bazel [79] reports a case of aplasia cutis congenita in one full-term twin, the other being a fetus papyraceus. The time of death of the fetus was estimated at about 4 months. It had its own amnion and chorion. The full-term twin, a boy, had a skin defect to the left and right of the navel, almost symmetrical, of the shape of a long rhombus, and reaching nearly to the posterior axillary line. The edge was formed of a whitish scarred stripe about 1 cm. wide. The rest of the surface was covered by a thin glistening skin which could not be removed. A granulating ulcer about as large as a penny was found in the center of the left side without epithelium. The healing ran a normal course, the ulcer being covered with epithelium on the fifth day after birth, and the red skin being considerably paler. The child was discharged as cured on the eleventh day.

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[78] Abt, I. A.: Congenital Skin Defects, Am. J. Dis. Child. **14**:113 (Aug.) 1917.

[79] Bazel, J.: Casop. Lek. cesk., Prague **61**:499 (June 3) 1922.

Shelmire[80] describes five cases of adenoma sebaceum occurring in one family, affecting the father, and four children, aged 12, 10, 6 and 3 years. The lesions arise chiefly from hypertrophy of the sebaceous glands. They vary from pinhead to pea size and are symmetrically distributed over the face. While many of the lesions are of the normal color of the skin, some are deep purple. The histologic picture of adenoma sebaceum shows that the sebaceous glands are increased in number and size and extend deeply into the corium. Some of the glands show cystic dilatation.

Josselyn[81] reports a rare skin disease in a child, 2½ years old, who presented brown round and oval areas irregularily scattered over the thorax, abdomen and back. The more exposed surfaces, such as the limbs and face, were not involved. The lesions, which were at first raised and looked like bee stings, gradually became flatter, and brown. The child was apparently in good health. The age of the patient; the mode of onset, chronicity and location, and the formation of wheals on rubbing were evidence in favor of urticaria pigmentosa. A condition closely resembling this one results from phenolphthalein poisoning, chronic, following long use of laxative phenolphthalein preparations. In this disease, the distribution is more general, the spots are yellow brown and no wheals are present. Treatment of urticaria pigmentosa is said to be of no use, the disease terminating at about the age of puberty. The usual treatment for urticaria may be tried.

Sibley[82] presented a girl of 5 years having monilethrix, the only one in her family affected. At birth, she had dark brown hair which was normal in appearance. At 1 month of age, the hair came out, and it had never grown properly since. It now had the appearance of flaxen tow, being from 1 to 2 inches (2.5 to 5 cm.) long on the vertex of the scalp, but only about one-eighth to one-fourth inch (0.3 to 0.6 cm.) in length over the occipital and parietal regions and the margin of the frontal region. The hairs were very brittle. The structural appearance of the eyelashes did not suggest monilethrix. The whole scalp presented the appearance of keratosis pilaris.

Golay[83] observed a girl with monilethrix for five years. The patient was born at full term. It was noticed that the scalp was dry and rough, and no hair could be seen on it. Rudimentary hairs began to appear toward the fifth month. The child is now 5 years old and shows a marked condition of keratosis pilaris. The hairs are dry, short

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80. Shelmire, J. B.: Adenoma Sebaceum, J. A. M. A. **71**:963 (Sept. 21) 1918.

81. Josselyn, R. B.: J. Maine M. A. **12**:53 (Sept.) 1921.

82. Sibley, W. K.: Proc. Roy. Soc. Med., London **14**:70 (June) 1921.

83. Golay, J.: Ann. de dermat. et syph. **3**:294 (June) 1922.

and brittle and have the beaded appearance which is characteristic of monilethrix. The eyebrows, eyelashes and hairs of the body are affected. The Wassermann reaction is negative. Thyroid extract alone or associated with other glandular extracts produces no improvement.

Ferreira [84] studied the incidence of mongolian spots in 485 infants. The races represented were the white and the black (mulatto and negro). Mongolian spots were borne by 5 per cent. of the whites, 63 per cent. of the mulattoes and 43 per cent. of the negroes. The sacral region and buttocks were the sites of selection. The spots rarely occurred elsewhere. They were usually single, rarely multiple. One case presenting eleven spots was observed.

Eyzaguirre [85] observed mongolian spots occurring in Peru. The modern coast dwellers of Peru are of mixed stock; while the people of the Andes represent the pure Peruvian stock. The blue mongolian spots are borne by 80 per cent. of the native children of both stocks, but they are rarely found where the white blood predominates. The spots occur more frequently in boys than in girls, and the younger the child the more distinct the spot is. The pigmentation does not remain longer than four years and often occupies the sacrococcygeal area, which is the area most notably pigmented in mammals. Histologically, large cells appear in the dermis, bearing melanin or chromatoblasts. The spots are hereditary and are transmitted according to the mendelian law. They are characteristic of the Indian and the Mongolian races, the incidence being 72.48 per cent. Boisserie-Lacroix [86] made similar observations on the occurrence of mongolian spots in 1,000 children in Bourdeaux.

Halez [87] makes some interesting remarks on the desquamative dermatosis of the skin. Erythema of the skin, with more or less desquamation, is not rare in young infants. It is often epidemic among nurslings, beginning as a redness about the mouth. The erythema gradually spreads all over the body and vesicles or bullae develop. Sometimes the mucous membranes are affected. The vesicles finally dry up and the skin desquamates in large flakes. Death occurs in about half the cases in from eight to fifteen days. The affection seems to be primary and is not preceded by seborrhea of the scalp, by intertrigo or by gluteal erythema. Staphylococci and an unidentified diplococcus are found in the vesicular liquid and sometimes in the blood. The appearance is similar to that of phemphigus.

The treatment of infantile desquamative erythemas is hygienic rather than medicinal. Cleanliness is important. Soiled diapers should be

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84. Ferreira, C.: Arch. de méd. d. enf. **25**:23 (Jan.) 1922.
85. Eyzaguirre, R.: Arch. de méd. d. enf. **25**:19 (Jan.) 1922.
86. Boisserie-Lacroix: J. de méd. de Bordeaux **94**:355 (June 10) 1922.
87. Halez, G.: Nourrisson **10**:6 (Jan.) 1922.

promptly changed. Bathing should be generally avoided, as it tends to irritate the skin. The infant may be bathed with a mixture composed of iodin, 1 gm., potassium iodid, 2 gm., and distilled water, 1 liter. The skin should be dried without rubbing and talcum dusted on.

Van Lohuizen[88] presented a new-born child with telangiectasia cutis and subcutis. These rare cutaneous changes are divided into two groups: (1) marble-like (veined) areas and (2) blue-red patches. The marble-like portions resembled the cutis marmorata of healthy nurslings, except that the phenomenon was more marked, the white patches between the meshes were larger and the limiting lines of the meshes were broader. The blue-red patches looked at first sight like vascular nevi. Their outlines were irregular, and the patches were not prominent over the skin. The skin presented prominent veins and also some small defects. The nose, lips, genital organs, ears, the volar surfaces of the hands and the plantar aspect of the feet were free from changes. The skin changes had persisted and existed for eighteen months after birth, but they were less marked.

The histologic examination of a speciman revealed a large number of vessels in the cutaneous and subcutaneous tissues. They were enlarged; but there was no other anomaly. The diagnosis, therefore, must be cutis marmorata telangiectasia congenita. The Pirquet and Wassermann reactions were negative. The nevi cannot be considered tumors. The most plausible hypothesis is that the skin anomaly was a developmental disturbance.

For many years, Lehnroff and Leiner[89] have noted an erythema occurring in children with endocarditis, with or without rheumatism. The disease is known as erythema annulare, a typical exanthem in endocarditis. This erythema is always of the same character and has probably been overlooked because of its delicacy and faintness. The erythema is so typical and constant that on it alone may be based the diagnosis of endocarditis. It appears at all ages in which joint diseases are seen but has not been observed in infancy.

The erythema does not appear at the onset of the rheumatism, but often develops after defervescence when the pallor and weakness lead to the suspicion of heart disease. Distinct endocarditis or suspicious cardiac murmurs were always found at the time of the eruption, the latter being the first sign of the disease in one case. The eruption is never seen in malignant endocarditis or endocarditis due to other infectious diseases (gonorrhoea, scarlatina, syphilis or sepsis).

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[88] Van Lohuizen, C. H. J.: Nederl. Tijdschr. v. Geneesk. **66**:1259 (April 1) 1922.

[89] Lehnroff, H., and Leiner, C.: Ztschr. f. Kinderh. **32**:46 (March 15) 1922.

The polymorphous exanthems described in rheumatism and endocarditis are never found simultaneously with erythema annulare. The latter is usually accompanied by other symptoms. The first efflorescences are small (1-3 mm.) rings of delicate rose, bluish or pale livid, few in number, over the trunk, especially the breast, upper half of the abdomen, the lateral part of the thorax and the back. The rings become more distinct if the child is uncovered for a time. They increase in size in a few days or hours, become confluent and form polycyclic figures. More rarely, they involve the extremities; most frequently the inner surfaces of the thigh, rarely the extensor surfaces. The face and mucosa are free. Edema, follicular hypertrophy, hemorrhages and itching are not observed, nor are scaling or pigmentation, after the eruption disappears. The eruption lasts only a few days and varies in distinctness. The intensity of the eruption bears no relation to the degree of the rheumatic process. Drugs can be definitely excluded in the etiology. Cultures from the blood and spots were negative. The absence of pustules with hemorrhages or necrosis argues against a metastatic bacterial focus.

Zurhelle[90] presented a boy, 13 years old, who showed the typical picture of parapsoriasis guttata with an extensive leukoderma. The individual efflorescences were brownish and covered by a firmly adherent lid-shaped scale. On lifting off the scale, there were no papillary hemorrhages such as are found in true psoriasis. The efflorescences were scattered over the whole back. The head was free, but the upper lids showed a few scales. There was also a marked leukoderma of the umbilicus and of the breast, extending to the stomach region and between the shoulder blades. The Wassermann reaction was negative. Spirochetes were absent and there were no other signs of syphilis.

With roentgen-ray treatment and the use of a salicylate salve, the efflorescences disappeared, but the leukoderma persisted. The case is noteworthy on account of the leukoderma and the localization of the efflorescences on the upper lids.

Gonella[91] studied skin pigmentation in thirty-three children and ten fetuses. Small specimens of skin were excised. This was generally carried out postmortem, but in a few cases a small amount of epidermis was removed in the living child. It was taken from the same region in all cases. The ages of the children varied from 8 months to 5 years. The youngest of the fetuses was 10 cm. long, the oldest was full-term. The specimens were hardened in formaldehyd. Sections were made with a microtome and were then treated with the dopa stain (dioxyphenylalanin), some with silver nitrate for four or five hours, without incubation. The reactions were on the average weaker than those for adults. A coherent line of pigmentation was found only in those children who had been cured of measles by means of irradiation or who had syphilitic exanthems and a particularly richly pigmented epidermis.

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[90] Zurhelle, E.: Dermat. Ztschr. **35**:338 (March) 1922.

[91] Gonella, M.: Jahrb. f. Kinderh. **48**:123 (May) 1922.

There was some pigmentation in all the skin specimens of the children. The fetuses presented various degrees of development of the epidermis, according to the age. Differences were also found between the still-born fetuses and those that had lived even for a short time. The pigmentation appears, therefore, to have some relation to extra-uterine life.

Schmidt[92] reports cases of four children of the same family with xanthoma. The condition developed in early life. The disease was most extensive in the eldest child. None of the children showed evidence of organic disease. The liver was normal. There was an increased cholestrin content of the blood in all of the patients. As the disease occurred before puberty, and as all the members of the family were affected, the author considers the condition as xanthoma juvenile familiare hereditarium. Very little is known as to the duration of hereditary xanthoma. It seems that hereditary xanthomatosis lasts throughout the patient's life without material changes in its extent or in the size of the individual lesions.

Junes and Buckwell[93] describe a case of xeroderma pigmentosum in a boy, aged 7 years, the exposed parts of whose body were covered with patches of lentigo. On the face and neck, there were red vascular macules, nevis sclerotic and atrophic areas, and subcutaneous nodules, which gave rise to ulceration. Keratotic formations were present about the left ear. The right cornea and conjunctiva were infiltrated and vision was reduced. A tumor was attached by a pedicle to the external quadrant of the left cornea. The anterior chamber was obliterated and the iris adherent to the posterior surface of the cornea. The tumor was removed and roentgen-ray treatment was instituted. Soft rays were employed, the intensity being 1 milliampere and the duration of exposure ten minutes.

Bechet[94] presented a boy of 13 years who had pityriasis rubra pilaris associated with dystrophia adiposogenitalis. The boy gave a history of a fall from a subway platform with a resulting burn from the third rail, involving the right scapular region. One month after the accident, the eruption appeared, first in scaly patches, which subsequently became keratotic. Later, the palms and soles became hyperkeratotic. The patient was undersized, with marked obesity. The genital organs were extremely infantile and atrophic. A large part of the trunk and thighs was covered with patches of aggregated red, acuminate papules, with hyperkeratosis of the pilosebaceous follicles. Biopsy made on a lesion on the shoulder showed marked thickening of the corneous layer of the epiderm, particularly at the mouths of the hair follicles, forming plugs. The sweat and sebaceous glands were few in number and small. The patient was given pituitary extract (posterior lobe) in one half grain tablets three times a day. There was marked and progressive improvement in both the eruption and the hypopituitary condition within a few weeks.

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[92] Schmidt, E.: Arch. f. Dermat. u. Syph. **140**:408 (June 10) 1923.

[93] Junes, E., and Buckwell, P.: Rev. tunis d. sc. méd. **16**:345 (Aug.) 1922.

[94] Bechet, P. E.: New York M. J. **116**:372 (Oct. 4) 1922.

Fol and Jaeger[95] report a case of *"creeping disease"* in a girl, 4 years old. On the buttocks, there appeared a reddish stripe, which became longer from day to day. When the child was taken to the hospital a month later, a tortuous line was found, which was disappearing at one end and advancing at the other. There were four zones: (1) a progressive zone, consisting of a simple red line on the skin; (2) a fresh reaction zone, consisting of a narrow central stripe covered with vesicles and passing into an erythematopapulous part; (3) a zone of regression, a brownish stripe with sharp boundaries without signs of inflammation, covered with crusts, and (4) a critical zone of small flat, livid scales. The parasite followed an irregular line and reached the anterior surface of the thigh, and seemed to advance more rapidly in the night, covering from 5 to 10 cm. daily. The parasite could not be isolated from the lesions. Retrogression of the symptoms followed within a short time under the use of disinfectants. Histologic examination of different zones of the affected skin showed that the course of the larva was blocked in skin layers of different depths, often at the boundary of the body of the papilla, but often also in the superficial layer of the epidermis.

Fox[96] recommends the use of mercury in the treatment of flat warts. Mercurous iodid in doses of one fourth grain, three times a day, is given internally. Fox remarks that, from his limited experience with mercury therapy of warts, there is no doubt that, in a certain percentage of cases, successful results can be obtained.

Senear and Fink[97] give an excellent treatise on hydroa vacciniforme seu aestivale, which is an interesting skin condition occurring chiefly in the spring and summer months. The disease usually begins in childhood. In practically all cases, the eruption is confined, at least during its height, to these seasons. March and April are the chief months for the onset of the annual attacks, with recurrences during the spring and summer months, or sometimes through the fall and winter. August and September are usually the latest months in which any considerable eruption is present. The reasons for the seasonal occurrences are obvious. During these months, the luminous intensity of the sun's rays are greatest.

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[95] Fol, P. M., and Jaeger, H.: Schweiz. med. Wchnschr. **52:**1011 (Oct. 12) 1922.

[96] Fox, Howard: Treatment of Flat Warts by Internal Administration of Mercury, Am. J. Dis. Child. **25:**55 (Jan.) 1923.

[97] Senear, F. E., and Fink, H. W.: Hydroa Vacciniforme Seu Aestivale, Arch. Dermat. & Syph. **7:**145 (Feb.) 1923.

Ehrmann [98] was the first author to study experimentally the effect of light on a patient suffering with hydroa vacciniforme. Using a Finsen light with a blue filter, he exposed parts of the skin normally covered by the clothes and was able to produce typical lesions which resulted in scar formation. Ehrmann concluded that short actinic rays not absorbed by blue glass but absorbed by red glass, acting on persons with an idiosyncrasy for these rays, produce the eruption. This conclusion has been verified several times by other writers, and leaves no doubt of the correctness of Ehrmann's [98] view. Further evidence of the origin from the chemical rays of the sun lies in the observation that, in hydroa vacciniforme, the lesions appear some hours after exposure to the sun's rays.

The question of the etiologic importance of atmospheric factors other than the actinic rays of the sun is still unsettled. In a number of cases, it has been stated that the wind is capable of exciting the eruption, although in these cases the presence also of the actinic rays of the sun could not be entirely ruled out.

The distribution of the eruption in hydroa vacciniforme is on the exposed parts of the body, but it should be understood that the predilection for these parts exists only because they are exposed to the light. It is probable that, in affected persons, the eruption might occur on any part of the cutaneous surface exposed to sufficiently intense sunlight. This has been demonstrated repeatedly, both clinically and experimentally. The parts affected most frequently are the ears, the face, especially the nose and the flush portion of the cheeks, and the dorsal surface of the hands. The cornea may be affected, also the mucous membrane of the mouth, and in one case, the tongue was involved.

The vacciniform type of eruption is the most characteristic form. In this type, erythematous lesions develop first, and on these appear transparent vesicles of a herpetiform character. At times, the lesions begin as hard nodules, which increase peripherally and gradually rise above the level of the skin. They may be single or more or less grouped. They vary from pinhead to pea size, but, through coalescence, they may form bullae. These lesions, if small and superficial, may dry up in a day or two, leaving a thin crust, or may rupture and leave a thicker, yellowish crust. The larger and more deeply seated lesions have at first a clear content, which may later become purulent or brownish. The center sinks in and a brownish or black crust, which gradually becomes larger peripherally, forms. At this stage, the lesions resemble closely a vaccination pustule, and like the latter, do not collapse when punctured, as dissepiments give it a multilocular character. In this type, the crust may not be shed for weeks. The lesions as a rule have an areola.

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[98] Ehrmann, S.: Arch. f. Dermat. u. Syph. **77**:163, 1905, quoted by Senear: Footnote 97.

Variations from the characteristic eruption may be of three types. In the first of these, the eruption is of a mild character. The lesions are papulovesicular, fairly superficial and never of the umbilicated type. The duration of the individual lesion is short. In spite of this, and without the aid of trauma or secondary infection, scarring is produced. The second group comprises those cases in which the lesions, covered with a thick yellowish crust, assume an impetiginous form. In several instances, this impetiginization has masked the essential picture, leading to error in diagnosis for a time. In the third form, the eruption is of a severe bullous variety. In many of the vacciniform cases, some bullae are present. This form is often difficult to diagnose, but histologic study of the skin confirms the diagnosis of hydroa vacciniforme.

Local symptoms are usually present. The outbreak is often preceded by sensations of burning or fulness in the affected parts. After the eruption is once established, the patient may suffer itching and occasionally pain, but frequently does not complain of any symptoms. In some cases, the attacks may be ushered in by general symptoms, such as chills, nausea, and at times, vomiting. Malaise and a slight temperature are the symptoms most frequently seen.

Senear and Fink [97] presented a case of hydroa vacciniforme occurring in a schoolboy, 11 years of age. The patient was first seen in July, 1921. The previous year he had a febrile condition, which was suspected of being typhoid fever, lasting from Thanksgiving to December. Shortly after this, he developed an eruption over the buttocks, which at first was thought to be due to some medicine which he had taken. This practically disappeared in about three weeks, but it recurred immediately, and soon healed under local treatment. In March, 1921, he developed an eruption on the ears. A short time later, the face and neck became involved, and there were a few lesions on the arms. This eruption consisted of vesicles, some of which became pustular. The lesions ruptured, became crusted and disappeared in a few weeks leaving small scars. New lesions had appeared in crops from time to time since then, all running the same course. When seen in July, the patient had a number of papulovesicular and pustular lesions in the butterfly area on the face, on the ears, the forearms and the buttocks. On the back of the hands, there were a number of pinhead size vesicles. The ears, face, back of the neck and backs of the hands showed a number of small white scars, which could scarcely be called vacciniform. The boy spent the remainder of the summer in Virginia, and, by avoiding exposure to the sun, he had been comparatively free from the eruption. He was seen again, March 15, 1922. The mother said that he had had no lesions during the winter but that about a week before he had gone on a "hike" with his Boy Scout company, the day being both sunny and windy. On the following day, the eruption appeared, preceded by itching and burning. It involved only the butterfly area of the face, the ears and the back of the hands. The eruption at this time consisted of pinhead size lesions, which had evidently been vesicular. The crusts were of a clean honey-colored appearance and not adherent. The lesions did not seem sufficiently severe to result in scar formation. No umbilicated lesions had been seen at any time. There was slight burning and itching with the outbreaks, not severe enough to cause scratching of the lesions, so the scarring could not be attributed to trauma.

In the treatment of hydroa vacciniforme, the list of applications used in an attempt to protect the skin is long, but none of them seem to have had any effect. Treatment has been of little avail, although ointments containing quinin or esculin have been reported as of value in some cases.

A CASE OF MENINGITIS DUE TO MICROCOCCUS CATARRHALIS *

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BOSTON

History.—S. J., a Jewish girl, aged 5 years, admitted to the pediatric service at the Boston City Hospital, March 2, 1923, two weeks previously had awakened at night with nausea and vomiting, a sore throat, and a temperature of 100 F. Five or six days before admission, she had a severe headache on the left side. associated with pain in the left ear, and became drowsy. The headache grew progressively worse and was present day and night. No history of convulsions or paralyses was obtained.

Physical Examination.—The child, a well developed and well nourished girl, was irritable and uncooperative. She breathed rapidly, and the face was flushed, the tongue coated, and the pharynx injected. Marked rigidity of the neck was present, with pain on the slightest motion. The Kernig sign was positive. The temperature was elevated, and the pulse and respirations were increased. Examination of the urine was negative. A lumbar puncture was made and a slightly cloudy fluid under increased pressure was obtained, containing 1,500 cells per cubic millimeter, of which 90 per cent. were polymorphonuclear and 10 per cent. mononuclear cells. The globulin was increased. The sugar content was 33.8 mg. per hundred cubic centimeters. Intracellular gram-negative diplococci were found and 30 c.c. of antimeningococcus serum was administered.

Course.—March 3: Lumbar puncture was performed twice and 30 and 25 c.c. of serum injected into the spinal canal.

March 4: Lumbar puncture was again performed twice and 25 and 10 c.c. of serum injected. The fluid was still cloudy, containing 1,620 cells, of which 88 per cent. were polymorphonuclear and 12 per cent. mononuclear. The globulin test remained positive.

March 5: No fluid could be obtained by lumbar puncture.

March 6: The laboratory reported that the organism was not agglutinated by the state antimeningococcus serum. The white cell count was 14,200. The patient's general condition remained about the same.

March 10: Slight improvement was reported, although the evening temperature continued to reach from 103 to 104 F. The white count was 20,000. No lumbar puncture had been attempted since March 5 on account of an area of infected skin on the back.

March 14: The Widal test was reported negative, the patient's general condition remaining about the same.

March 16: A slightly cloudy fluid was obtained, containing 1,350 cells, of which 90 per cent. were polymorphonuclear and 10 per cent. mononuclear. The fluid was cultured and *Micrococcus catarrhalis* was found.[1] The white cell count was 11,900.

March 22: Physical examination disclosed no change in signs, although the patient was losing weight rapidly. The fundi were negative.

March 24: Lumbar puncture yielded an opalescent fluid, under normal pressure, containing 4,250 cells, of which 85 per cent. were polymorphonuclear.

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* Received for publication, Sept. 10, 1923.

* From the pediatric service of the Boston City Hospital.

[1] The bacteriologic findings are summarized chiefly from work done in the Pathological Laboratory of the Boston City Hospital by Marion E. Lamb. Some of the attempts to agglutinate the organisms with antimeningococcic horse serums were carried out at the Antitoxin and Vaccine Laboratory of the Massachusetts Department of Public Health.

March 30: The fluid contained 3,500 cells, 82 per cent. polymorphonuclear. Stiffness of the neck and a double Kernig sign persisted. The white cell count was 21,550.

April 3: Prolonged coughing spells were noted, with a suggestive whoop.

April 7: The paroxysmal cough was noted as being more severe and associated with vomiting. The patient was much weaker, showing marked loss of weight and turgor. The neurologic signs were unchanged. Opalescent fluid under normal pressure, obtained by lumbar puncture, contained 2,486 cells, of which 78 per cent. were polymorphonuclear and 22 per cent. mononuclear. The globulin test was positive.

April 17: A small amount of fluid was obtained. The sugar content was 45.1 mg. per hundred cubic centimeters. An insufficient amount was obtained for further examination.

April 19: The white count was 68,540.

April 23: The temperature was noted as having been normal for several days. The meningitic signs at this time were subsiding, but the pertussis continued severe and was associated with rapid loss of weight and strength.

May 5: The left ear began to discharge. Vomiting had ceased, but the cough continued. Practically no nourishment was being taken voluntarily and nasal feedings were instituted.

The course of the disease continued unchanged until the death of the patient, May 29, eighty-eight days after admission to the hospital and about 102 days after the onset of symptoms. No necropsy could be obtained.

Dr. Josephine B. Neal of the Bureau of Laboratories of the New York Department of Health, in a personal communication, reports a case of *Micrococcus catarrhalis* meningitis, first seen, Feb. 8, 1922, when the patient was 7 weeks old. Lumbar and ventricular puncture yielded a cloudy yellow fluid, and antimeningococcus serum was given The organism was cultured and found to be *Micrococcus catarrhalis,* and an autogenous vaccine was made and injected intraventricularly. Although some clinical improvement took place, the outcome of the disease was not affected and the infant died the following month.

Two other cases of *Micrococcus catarrhalis* meningitis have been reported by Cassoute and Gibaud [2] and Cot and Robert.[3] In the case reported by Cot and Robert, *Enterococcus* and *Micrococcus catarrhalis* were cultured from the spinal fluid. The meningitis was mild, but, on the thirty-second day, orchitis of the mumps type developed.

A case of this nature is interesting partly from its rarity but more especially on account of the twofold lesson it teaches: (1) it is self-evident that all intracellular gram-negative diplococci found in the spinal fluid are not necessarily meningococci; (2) the spinal fluids from all cases of purulent meningitides should be cultured and agglutination tests made with therapeutic serum in order that a specific serum for the organism may be obtained and used in cases in which the disease is due to the meningococcus.

It is well known that a number of strains of meningococcus exist, grouped according to agglutinin and tropin reactions. At the present time, according to Blackfan,[4] the determination of the agglutinin content of the serum is considered, in this country, the most reliable method for the standardization of antimeningococcus serums, as it has been demonstrated that a high agglutination titer is usually accompanied by a strong complement-binding power and a high opsonic index. Serum showing a high agglutination titer for the meningococci isolated from the patient's cerebrospinal fluid, as a rule, gives good therapeutic results. Serum used in treatment should contain antibodies for the two main types of organism and the subtypes.

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[2] Cassoute and Gibaud: Marseille méd. **62**:783, 1920.

[3] Cot and Robert: Paris méd. **11**:318 (Oct. 22) 1921.

SUMMARY

A case of *Micrococcus catarrhalis* meningitis, complicated by pertussis and acute otitis media, ended fatally. Three other cases due to the same organism have been collected.

Culturing and testing of the agglutinability of the organism in cases of meningococcus meningitis are important, in order that a specific serum may be used in treatment.

Smears made from the spinal fluid removed at different times and stained by Gram's method consistently showed numerous pus cells, chiefly polymorphonuclear leukocytes, with many intracellular and extracellular gram-negative biscuit-shaped diplococci.

Cultures on blood agar showed abundant growth after eighteen hours' incubation at 37.5 C. The individual colonies were round (from 2 to 5 mm. in diameter), raised, glistening, moist, whitish and somewhat translucent. In the majority of instances, the growth was confluent. There was no hemolysis. The colonies resembled those of the bacilli of the colon group except that they were slightly less translucent. Cultures on plain agar and dextrose agar were identical with those described above. Eighteen-hour plain bouillon cultures showed a general clouding of the medium with a settling out of large numbers of the organisms in the bottom of the tube.

Cultures in Hiss serum (human) water mediums containing 1 per cent. of the various sugars (dextrose, maltose, levulose, saccharose and galactose) all showed growth without the production of acid or gas at the end of forty-eight hours. Smears made from the cultures and stained by Gram's method consistently showed gram-negative diplococci, irregular in size and intensity of staining, and with a tendency to arrange themselves in tetrads.

Attempts to agglutinate salt solution suspensions of the organisms with dilutions (from 1:100 to 1:1,600) of various lots of antimeningococcic horse serum of standard potency were unsuccessful. Likewise, serum obtained from the patient failed to agglutinate the organisms.

Blood cultures taken at different times during the course of the disease were negative.

On the basis of the morphologic, cultural and serologic findings, a bacteriologic diagnosis of *Micrococcus catarrhalis* was made.

270 Commonwealth Avenue.

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[4] Blackfan, K. D.: Medicine **1**:139 (May) 1922.

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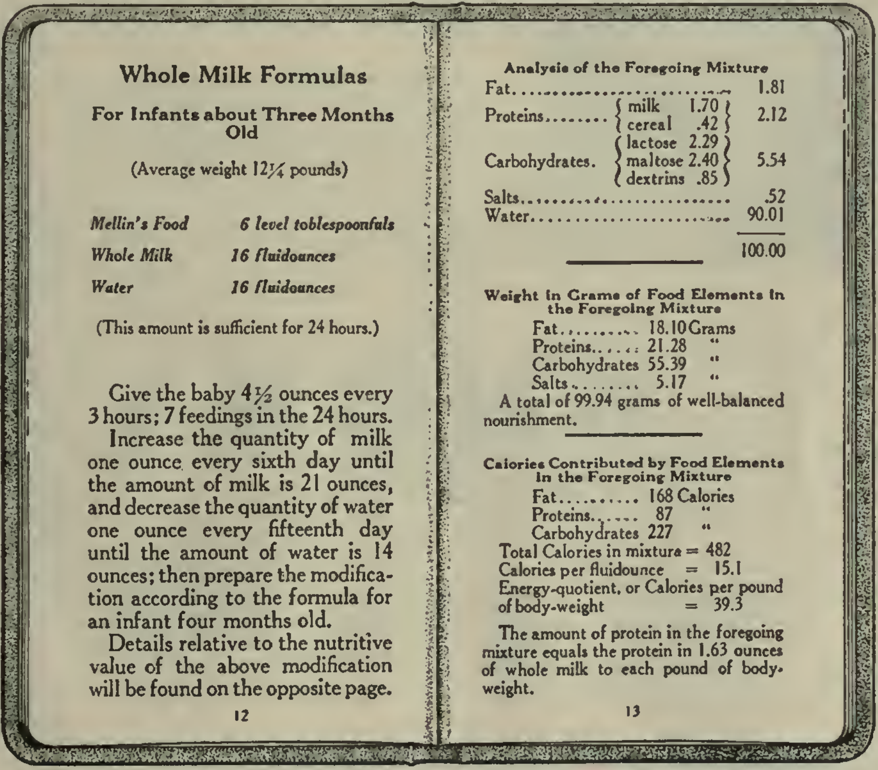
To give some idea of the magnitude of this new work and how well it keeps step with the progress in infant feeding, we display below two pages of this 80-page book. It will be noted that the formula adjusted to age and weight, together with simple instructions for progressive changes, is given on the left-hand page, and on the right practically every detail relative to the balance of nutrition is stated. This plan is followed throughout the book, thus giving information of daily usefulness not accessible in any other work of this nature.



Whole Milk Formulas

For Infants about Three Months Old

(Average weight 12¼ pounds)

Mellin's Food	*6 level toblespoonfuls*
Whole Milk	*16 fluidounces*
Water	*16 fluidounces*

(This amount is sufficient for 24 hours.)

Give the baby 4½ ounces every 3 hours; 7 feedings in the 24 hours.

Increase the quantity of milk one ounce every sixth day until the amount of milk is 21 ounces, and decrease the quantity of water one ounce every fifteenth day until the amount of water is 14 ounces; then prepare the modification according to the formula for an infant four months old.

Details relative to the nutritive value of the above modification will be found on the opposite page.

12

Analysis of the Foregoing Mixture

Fat		1.81
Proteins	milk 1.70 cereal .42	2.12
Carbohydrates.	lactose 2.29 maltose 2.40 dextrins .85	5.54
Salts		.52
Water		90.01
		100.00

Weight in Grams of Food Elements in the Foregoing Mixture

Fat	18.10 Grams
Proteins	21.28 "
Carbohydrates	55.39 "
Salts	5.17 "

A total of 99.94 grams of well-balanced nourishment.

Calories Contributed by Food Elements in the Foregoing Mixture

Fat	168 Calories
Proteins	87 "
Carbohydrates	227 "

Total Calories in mixtura = 482
Calories per fluidounce = 15.1
Energy-quotient, or Calories per pound of body-weight = 39.3

The amount of protein in the foregoing mixture equals the protein in 1.63 ounces of whole milk to each pound of body-weight.

13

Special formulas calculated to meet conditions other than normal, with suggestions for their practical application, broaden the scope of the work, which in its entirety marks a distinct advance toward a better understanding of infants' nutrition.

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2. Their flesh is firm, and they develop normally.
3. They are normally free from rickets and spasmophilia.
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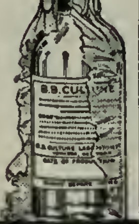

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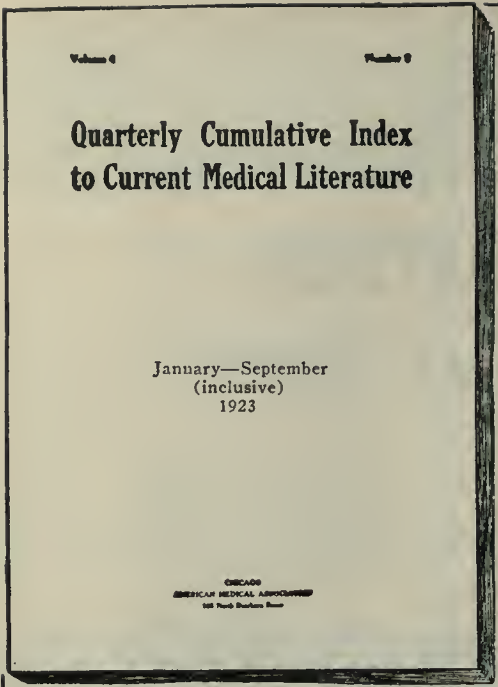

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